THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JULY, 1933.

ORIGINAL ARTICLES.

ON THE INHERITANCE OF DIABETES MELLITUS.

I. AN ANALYSIS OF 675 FAMILY HISTORIES.*

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THE suggestion has been made that the potentiality for developing diabetes may be inherited as a simple Mendelian recessive (White[1]). No definitive conclusions were possible, however, because the data in the instance cited were deficient in certain information and no control population was available. We have accordingly collected the family histories of 523† diabetic patients appearing at the Joslin Diabetic Unit from July, 1932, to October, 1932, and control histories were obtained from 153 non-diabetic patients.

The data were collected by questioning the patient, and in a large number of cases at least one near relative. Recording was made of all facts that appeared to be pertinent for this or succeeding

* Since this manuscript was received, an article by William Allan, on Heredity in Diabetes, has appeared in the *Annals of Internal Medicine* (1933, **6**, 1272) reiterating Dr. White's suggestion that potentiality of diabetes may be transmitted as a recessive unit character. We are glad that his suggestion that a genetic study be carried out on less meager data than he was able to collect can be so promptly met.—EDITOR'S NOTE.

† Actually 531 successive cases were recorded; 8 were discarded because of inadequate or faulty recording.

surveys, and a card was made out for each patient, as presented in Fig. 1. These records were obtained in part from patients returning for periodic examinations and whose family histories were already somewhat known, and in part from patients appearing for the first time. In the case of the former group previous records provided a check on the accuracy of the histories. We were especially particular to obtain the correct age of all living siblings and parents and the age at death of all dead siblings and parents, for, as our later analysis will show, any detailed treatment must be based on the division of these relatives into certain age groups.

FIG. 1.—THE CASE RECORD OF EACH DIABETIC PATIENT.

Patient.						Siblings.					
Case No.	Sex.	Date of personal observation.	Onset age.	Duration of diabetes.	Present age.	Present age. Males.	Present age. Females.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.

Mother.					Father.				
Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.	Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.

Spouse.		Children.		Spouse and children.				
Present age.	Age at death.	Present age.	Age at death.	Onset age.	Duration of diabetes.	Fatal date.	Other diabetic relatives.	Remarks.

In Table 1 we have assembled the incidence data by decades for our control and for our diabetic populations. We have compared the incidence in the parents and siblings of each patient because these are the most accurately recorded. Data on other relatives are much less reliable and their significance more obscure. The crude figures are as follows: in 523 diabetic families there were reported 187 diabetic relatives other than parents and siblings in 110 families, or 22.94 per cent of the families with diabetic blood relatives; in the 153 non-diabetic families 16 families or 10.46 per cent reported 21 blood relatives with diabetes. The difference between the incidences among these relatives in the two groups is therefore 12.48 per cent; the probable error of this difference is 2.08 per cent, and the difference divided by the probable error is 6. The odds are 19,300 to 1 against such a difference having arisen as a result of chance alone. We may, therefore, say that there has been reported in our diabetic families a significant excess of families with diabetic blood relatives (other than parents and siblings) as compared with the control families.

A similar excess of diabetic siblings and parents is apparent on inspection of Table 1. It will be noted that our control population contains, particularly among the siblings, relatively more persons in the early decades than does the diabetic population. The proper comparisons must therefore be made between the same decades and

not for the whole population, since diabetes incidence changes from decade to decade, rising to a maximum at middle age and then declining. In this and in all succeeding tables the age at death of dead persons has been taken at present age; obviously the opportunity for developing diabetes is limited to the years during which an individual is alive.

TABLE 1.—COMPARATIVE INCIDENCE OF DIABETES IN PARENTS AND SIBLINGS OF A CONTROL AND A "DIABETIC" POPULATION.*

Decade.	"Diabetic" population.			Control population.			"Diabetic" population.			Control population.		
	Diabetic parents.	Non-diabetic parents.	Per cent diabetic.	Diabetic parents.	Non-diabetic parents.	Per cent diabetic.	Diabetic siblings.	Non-diabetic siblings.	Per cent diabetic.	Diabetic siblings.	Non-diabetic siblings.	Per cent diabetic.
1	..	..	..	..	..	..	4	243	1.46	0	90	0.0
2	..	..	..	..	..	..	7	141	4.73	1	90	1.11
3	0	16	0.0	0	6	0.0	3	216	1.37	0	120	0.0
4	4	119	3.25	0	14	0.0	7	207	3.27	1	104	0.96
5	6	134	4.29	0	54	0.0	11	259	4.07	0	94	0.0
6	20	153	11.56	1	76	1.39	26	319	6.96	0	77	0.0
7	32	194	14.16	2	62	3.23	32	224	12.50	2	44	4.55
8	18	180	9.09	3	56	5.35	10	92	9.80	0	23	0.0
9	5	121	3.97	0	29	0.0	0	8	0.0	0	5	0.0
10	1	29	8.33	0	3	0.0						
Totals	86	946	8.33	6	300	1.96	100	1709	5.85	4	647	0.62

* Several parents in each group whose ages were unknown have been omitted from this table.

A cursory inspection of Table 1 reveals that in every decade excepting the 3d in the parent population and the 9th in the sibling population, the diabetes incidence in the control group is on a percentage basis *less* than in the diabetic group, and in the two exceptional decades the incidence is the same, *i. e.*, 0.0 per cent. Now if the two populations were not significantly different as regards the incidence of diabetes we would expect the relative percentage of diabetics in each decade to fluctuate, to be higher now in one population, now in the other. The probability that in any decade one population will show a lesser incidence than the other is of course $\frac{1}{2}$, and the probability of an equal or higher incidence is also $\frac{1}{2}$. We can calculate the probability that in the 17 decades recorded (*i. e.*, 8 among the parents and 9 among the siblings) only 2 should show an equal (or greater) incidence in the control population, by the theorem which states that

$$P_m(n) = C_n^m p^n (1-p)^{m-n} \qquad (1)$$

where P is the probability we are seeking, m the number of trials, *i. e.*, the total number of decades, n the number of times that an equal or greater incidence occurs, and p the chances of occurrence. This becomes then

$$P_m(n) = C_2^{17} (0.5)^2 \times (0.5)^{15}$$
$$= 136 \times 0.25 \times 0.00003055$$
$$= 0.001038$$

The consistent lesser incidence of diabetics *per* decade in the control population could thus arise by chance alone once in 1000 trials. As we shall examine into the probability of various incidences hereafter, it may be well to state now that a value of P below 0.01 in the type of instance we shall examine is ordinarily taken to indicate a statistically significant deviation from random occurrence.

Our first examination, then, leads to the conclusion that there is a statistically significant excess of diabetic parents and siblings in our diabetic population as compared with the control population. We may proceed to determine the statistical significance of the difference in incidence in the 2 groups of parents and the 2 groups of siblings separately by the use of the χ^2 method. We are now interested, essentially, in determining the independence of our two populations and not in explaining this presumed independence. Accordingly we can calculate an "expected" incidence of diabetics for each decade by taking the known total number of diabetics and non-diabetics and allocating them in proportion to the total number of individuals in that decade in each population. This involves the calculation of expectancy for each decade of a 2 by 2 classification of the type described by Fisher[2] (pp. 85 and *ff.*). The expected values so calculated are listed in Table 2. The value of $\chi^2 = 18.366$ for the parents gives a probability of 0.0095, the $\chi^2 = 22.153$ gives for the siblings a probability of 0.0047, and each of these probabilities indicates a significant excess of diabetics in the diabetic populations.

The determination that we have presented of a statistically significant excess of diabetic relatives in the families of diabetic patients affords, of course, no hypothesis to account for the excess. If diabetes were an infectious disease we might advance the notion that a greater liability to infection exists in the families of the diabetic patients. Or we might suppose that a certain dietary régime leading to the eventual manifestation of diabetes is characteristic of diabetic families. We propose, however, to examine the hypothesis that the potentiality for developing diabetes is inherited as a simple Mendelian recessive, so that all persons capable of developing diabetes may be designated as *mm*. Non-diabetics are either *MM* or *Mm*. Only three types of matings can produce *mm* offspring. These are:

(1) $Mm \times Mm = 1\ MM : 2\ Mm : 1\ mm$
(2) $Mm \times mm = 1\ Mm : 1\ mm$
(3) $mm \times mm = 1\ mm$

Accordingly we may classify our families at once into these 3 groups: (1) both parents non-diabetic, (2) one parent diabetic, (3) both parents diabetic. In the last group we have 2 (possibly 3) matings, and except to mention now that the occurrence of diabetes in the offspring is not inconsistent with our Mendelian hypothesis we

TABLE 2.—COMPARISON OF OBSERVED AND "EXPECTED" INCIDENCE IN A CONTROL AND A "DIABETIC" POPULATION.

	"Diabetic" population.				Control population.					"Diabetic" population.				Control population.				
Decade.	Diabetic parents, observed.	Non-diabetic parents, observed.	Diabetic parents, expected.	Non-diabetic parents, expected.	Diabetic parents, observed.	Non-diabetic parents, observed.	Diabetic parents, expected.	Non-diabetic parents, expected.	Deviation.	Diabetic siblings, observed.	Non-diabetic siblings, observed.	Diabetic siblings, expected.	Non-diabetic siblings, expected.	Diabetic siblings, observed.	Non-diabetic siblings, observed.	Diabetic siblings, expected.	Non-diabetic siblings, expected.	Deviation.
1	..	..	...	....	..	..	..	...	..	4	243	2.93	244.07	0	90	1.07	88.93	1.07
2	..	..	...	....	..	..	..	...	..	7	141	4.95	143.05	1	90	3.05	87.95	2.05
3	0	16	0.0	16.00	0	6	0.0	6.00	0.0	3	216	1.94	217.06	0	120	1.06	118.94	1.06
4	4	119	3.59	119.41	0	14	0.41	13.59	0.41	7	207	5.37	208.63	1	104	2.63	102.37	1.63
5	6	134	4.33	135.67	0	54	1.67	52.33	1.67	11	259	8.16	261.84	0	94	2.84	91.16	2.84
6	20	153	14.53	158.47	1	76	6.47	70.53	5.47	26	319	21.26	323.74	0	77	4.74	72.26	4.74
7	32	194	26.50	199.50	2	62	7.50	56.50	5.50	32	224	28.82	227.18	2	44	5.18	40.82	3.18
8	18	180	16.18	181.82	3	56	4.82	54.18	1.82	10	92	8.16	93.84	0	23	1.84	21.16	1.84
9	5	121	4.06	121.94	0	29	0.94	28.06	0.94	0	8	0.0	8.00	0	5	0.0	5.00	0.0
10	1	29	0.91	29.09	0	3	0.09	2.91	0.09									
Totals	86	946	70.10	961.90	6	300	21.90	284.10	15.90	100	1709	81.59	1727.41	4	647	22.41	628.59	18.41

χ^2 = 18.366
P = 0.0095

χ^2 = 22.153
P = 0.0047

shall omit them from further consideration. In the first group we have 440 families, and in the second 81 families.

The reasons why we at once entertain this hypothesis rather than the hypothesis of dominance are: (1) The genealogies that we have available indicate that the disease may skip one or more generations, and the genealogies in the literature generally support this notion (see Baur, Fischer, and Lenz,[3] pp. 352–354 and the discussion of the literature in this paper); (2) on an hypothesis of dominance at least one parent in each mating should be diabetic or potentially diabetic. When one considers the ages of these parents and the ordinary age-incidence relations of diabetes the percentage of diabetic parents is much too small to admit an hypothesis of dominance except on special assumptions.

Omitting for the moment any discussion of the possibility that some of the parents classed as *Mm* are genetically *mm*, let us see how the incidence of diabetes among the children accords with the Mendelian expectation.

Since each of the families was chosen because at least one diabetic child had been identified, the Mendelian expectation of *mm* among the children becomes: $\frac{p}{1-(q)^n}$, where p is the probability of an *mm* individual appearing, q the probability of an *mm* individual not appearing, and n is the number of children *per* family. Thus, in a cross of $Mm \times Mm$ where we have one diabetic patient and 5 siblings the expectation of *mm* individuals is:

$$\frac{1/4}{1-(3/4)^6} = 30.41 \text{ per cent}$$

We actually have 38 families of 6 children each in our $Mm \times Mm$ cross. Of the 228 children we would expect 30.41 per cent or 69.33 to be *mm*. We have actually identified 38 of these as patients so that we would expect 31.33 *mm* individuals among the siblings. These expected *mm* individuals should be distributed among the various decades in proportion to the total number of persons in each decade; thus in the 1st decade there are 23 of these siblings or 12.11 per cent; accordingly we would expect 12.11 per cent of 31.33 or 3.79 *mm* individuals in the 1st decade. Applying these methods throughout, we can calculate the expectation of *mm* individuals for each decade in all the various-sized families, and by collecting the data arrive at an expectation *per* decade for the whole population of siblings in each of the two crosses. The patients are omitted from our tabulations and subsequent calculations since they serve merely to bring a given family into our tables.

The expected numbers of *mm* individuals do not represent actual diabetics, but only persons capable of developing diabetes. To calculate the actual number of *mm* individuals identifiable as diabetics we must have recourse to the age-indicence tables. Our final calculations depend upon one major assumption, namely, that

potential diabetics before they develop diabetes are subject to the same chances of death as are other members of the general population. If this be granted as a reasonable assumption, and there is no very definite evidence to the contrary, we can calculate from the ordinary life tables and the tables giving the age-incidence relations of diabetes, the proportion of potential to identifiable diabetics for each decade. This has been done in Table 3, using Glover's tables* for the 1910 population of the United States, and diabetes incidence data from three sources: (1) The first 6000 cases of Dr. Elliott P. Joslin; (2) the data of Adams[4] and (3) the actual incidence among the patients used in this study. The first group of cases were assembled between 1898 and 1926, and the life tables of the year 1910 are perhaps justifiably applicable to them. The data of Adams were collected at the Mayo Clinic and may be taken to apply fairly generally. The incidence data for this population are employed for reasons which will be given later.

TABLE 3.—AGE INCIDENCE AND POTENTIAL DIABETICS.

Decade.	Per cent surviving (Glover, 1910).	Per cent diabetics appearing among all identified (Joslin).	Relative number of potential diabetics.	Total potential and diabetic.	Per cent identified.	Incidence data (Adams).	Total potential and diabetic.	Per cent identified.	Incidence data (this population).	Total potential and diabetic.	Per cent identified.
1 . . .	82.46	4.57	165.49	170.06	2.69	4.3	168.78	2.55	8.65	164.28	5.27
2 . . .	97.11	6.52	154.19	160.71	4.06	6.1	159.73	3.82	12.88	151.13	8.52
3 . . .	94.64	8.09	137.84	145.93	5.54	9.5	145.40	6.53	9.62	130.84	7.35
4 . . .	92.43	12.94	114.47	127.41	10.16	12.3	125.61	9.79	9.81	112.04	8.76
5 . . .	89.18	23.70	78.38	102.08	23.22	19.7	101.05	19.50	18.46	91.17	20.25
6 . . .	81.87	27.18	36.99	64.17	42.36	27.4	66.60	41.14	24.04	59.53	40.38
7 . . .	66.13	13.73	10.73	24.46	56.13	18.2	25.92	70.22	13.85	23.47	59.01
8 . . .	40.55	3.10	1.25	4.35	71.26	2.4	3.13	76.68	2.50	3.90	64.10
9 . . .	13.62	0.17	0.0	0.17	100.00	0.1	0.10	100.00	0.19	0.19	100.00

The relative numbers of potential diabetics are determined from Glover's survival data as follows: In decade 9, 0.17 diabetics *per* 100 appear (Table 3, column 2). These represent 13.62 per cent of the persons alive in the previous decade (Table 3, column 1) who were capable of developing diabetes, but were not identified. Since 0.17 = 13.62 per cent, 1.25 = 100 per cent, *i. e.*, 1.25 potential diabetics (Table 3, column 3). These 1.25 potential diabetics, plus the 3.10 identified diabetics give 4.35 individuals in the 8th decade (Table 3, column 4) who, on our hypothesis, are all *mm*. The number of potential diabetics required to produce these 4.35 individuals is again calculated from the general survival data, and so on for each decade.

* Strictly, these tables should be corrected for the contribution of diabetes to each decade as a cause of death. Such correction is unnecessary in view of the slight alteration that would ensue.

It will be seen from an inspection of Table 3 that the computations derived from these various sources agree fairly well. We have in addition used the age-incidence data for Dr. Joslin's last 4000 cases, and for cases 7001 to 8000, and find no noteworthy differences between these incidence data and those presented in Table 3. We have also employed the Massachusetts life tables for 1900 in calculations with Dr. Joslin's data, since a good number of his cases were assembled from Massachusetts. These calculations are not presented as they do not differ significantly from the figures obtained by the use of Glover's tables.*

TABLE 4.—THE EXPECTED AND OBSERVED INCIDENCES OF DIABETICS IN THE SIBLINGS OF PATIENTS WITH BOTH PARENTS NON-DIABETIC (I. E., MM × MM).

Decade.	Potential diabetics expected.	Per cent identifiable (Joslin, U. S. A.).	Number identifiable.	Number observed.	Total number of siblings.	Number identifiable (Adams, U. S. A.).	Number identifiable (this population, U. S. A.).
1	34.74	2.69	0.93	3	209	0.88	1.83
2	21.59	4.06	0.88	6	134	0.82	1.84
3	32.41	5.54	1.80	1	196	2.12	2.38
4	28.15	10.16	2.86	6	168	2.76	2.47
5	35.44	23.22	8.23	7	210	6.91	7.18
6	46.81	42.36	19.83	14	281	19.26	18.90
7	33.19	56.13	18.63	20	201	23.31	19.59
8	14.31	71.26	10.20	7	88	10.97	9.17
9	1.32	100.00	1.32	0	8	1.32	1.32
Totals . . .	247.96	....	64.68	64	1495	68.35	64.68
Deviation . .	....	....	0.68	....	....	4.35	0.68
Probable error .	....	....	±5.31	....	....	±5.45	±5.31
Deviation / Probable error .	....	....	0.13	....	....	0.80	0.13

We may now calculate the expected number of *mm* individuals in each decade actually identifiable as diabetics by multiplying the Mendelian expectation by the expectation of identification. Thus in the cross *Mm* × *Mm* in the first decade we expect 34.74 *mm* individuals (Table 4, column 2). On the basis of Joslin's tables 2.69 per cent of these or 0.93 individuals should be identified as diabetics. The observed and expected numbers of diabetics *per* decade calculated in this way are presented in Tables 4 and 5 for the crosses *Mm* × *Mm* and *Mm* × *mm* respectively. The totals agree remarkably well, in fact somewhat better than one would expect by chance alone regardless of the source of the incidence data. But when the

* One might conceivably employ a life table constructed from the data of this population itself, but such a procedure is open to numerous objections, *e. g.*, the probability of high infant mortality in children of diabetic mothers, the debatable question of the inclusion of the parents, and the obvious limitations of a relatively small population.

data are examined decade by decade it is at once obvious that there is an excess of diabetics in the first few decades when we derive our expectations from Joslin's or Adams' data. It happens that we have in our population a larger proportion of younger patients than ordinarily appear in diabetic populations generally. If there were a positive correlation between the ages of onset of diabetes in siblings, then we would expect such an excess of diabetics in the earlier decades. For that reason we have employed the incidence data of this population in calculating the proportions of identifiable diabetics (see Table 3, last 3 columns, and the last columns of Tables 4 and 5). Actually, we do find that employing the diabetes incidence among the patients of this population better meets the expectation for the earlier decades than do the more general data of Joslin or Adams.

TABLE 5.—THE EXPECTED AND OBSERVED INCIDENCES OF DIABETICS IN SIBLINGS OF PATIENTS WITH 1 DIABETIC PARENT (I. E., Mm × mm).

Decade.	Potential diabetics expected.	Number identifiable (Joslin).	Number observed.	Total number siblings.	Number identifiable (Adams).	Number identifiable (this population).
1	15.83	0.43	1	38	0.40	0.83
2	5.58	0.23	1	14	0.21	0.48
3	9.50	0.53	2	23	0.34	0.70
4	18.32	1.86	1	46	1.79	1.60
5	23.32	5.41	3	58	4.55	4.72
6	25.39	10.76	12	62	10.45	10.25
7	18.66	10.47	9	47	13.10	11.01
8	4.43	3.16	3	11	3.40	2.84
Totals	131.03	32.85	32	299	34.24	32.43
Deviation	....	0.85	....	....	2.24	0.43
Probable error	....	±3.65	....	....	±3.71	±3.63
$\frac{\text{Deviation}}{\text{Probable error}}$	....	0.23	....	....	0.60	0.12

For testing the agreement between expectation and observation in each decade we have computed the probabilities of agreement from the formula

$$P = (p)^D \times (q)^R \times \frac{\lfloor n}{\lfloor D \, \lfloor R}$$

Where D is number of non-diabetics observed, p the expectation of non-diabetics, R the number of diabetics observed, q the expectation of diabetics, and n the total number of individuals observed. This formula is particularly applicable to ratios involving small numbers (see Warwick[5]). The values of P *per* decade for $Mm \times Mm$ and $Mm \times mm$ combined are given in Table 6. Since any value of P below 0.01 may be taken as showing a significant deviation

from expectation, it will be noted that only in the second decade is there any significant departure from expectation. This is not surprising when we consider that a disproportionate number of diabetic patients in our population are present in that decade.

TABLE 6.—THE PROBABILITIES (P) OF THE OBSERVED RATIOS IN EACH DECADE CALCULATED ON THE BASIS OF THE EXPECTED RATIOS FOR THE CROSSES Mm × Mm AND Mm × mm COMBINED.

Decade.	No. of diabetic siblings observed.	Total number of siblings.	No. of diabetic siblings expected (Joslin).	P (Joslin).	No. of diabetic siblings expected (Adams).	P (Adams).	No. of diabetic siblings expected (this population).	P (this population).
1	4	247	1.36	0.0362	1.28	0.0319	2.66	0.1483
2	7	148	1.11	0.0001	1.03	0.0000	2.32	0.0066
3	3	219	2.33	0.2111	2.46	0.2245	3.08	0.1800
4	7	214	4.72	0.0922	4.55	0.0802	4.07	0.0636
5	10	268	13.64	0.0722	11.46	0.1137	11.90	0.1094
6	26	343	30.59	0.0534	29.71	0.0644	29.15	0.0658
7	29	248	29.10	0.0781	36.41	0.0301	30.60	0.0747
8	10	99	13.36	0.0638	14.37	0.0564	12.01	0.1068
9	0	8	1.32	0.2364	1.32	0.2364	1.32	0.2364

Taken as a whole these data meet the requirements of the hypothesis set. This, on the face of it, is rather surprising, for our test of the hypothesis depends on the proportion of diabetic siblings in the two crosses *Mm* × *Mm* and *Mm* × *mm*, and our information about the presence of diabetics among these siblings depends upon the knowledge of the patient questioned. It seems not unreasonable to suppose that in a number of instances diabetic siblings exist who have not been recorded either because the patient (or any other relative questioned) simply did not know that his or her sibling had the disease, or because in certain instances diabetes may have been the cause of a death and not recognized as such. We have, in small measure, corrected for the latter possibility, for 6 of the siblings listed as diabetics in our tables presented symptoms of death so obviously the result of diabetes that they were at once so recorded, but it was impossible in many cases to obtain any reliable account of the ills and health of siblings.

Opposed to the probability that a number of diabetic siblings have escaped recording is the probability that a number of parents listed as heterozygotes (*Mm*) are really homozygotes (*mm*). The presence of genetically *mm* parents here classed as *Mm* would, of course, increase the expectation of *mm* offspring. The question then becomes: would the increased expectation of *mm* siblings due to the presence of unidentified but genetically *mm* parents seriously disturb our ratios, and to what extent would this increased expectation be balanced by the presumable presence of unidentified diabetics among siblings? A single illustration will suffice.

Let us suppose that in the 440 crosses listed as *Mm* × *Mm* 80 are really *Mm* × *mm*, and that these matings produce the average number of diabetic children observed, *i. e.*, 3.398 *per* family or 272 children. Our calculated general expectation of diabetics in the *Mm* × *Mm* crosses is 4.35 per cent (*i. e.*, about 65 diabetics in 1495, see Table 4), so that presumably we would expect 11.83 diabetics in these 272 siblings. In the *Mm* × *mm* group our average expectation of diabetics is 11.04 per cent (*i. e.*, about 33 out of 299 siblings) so that we would expect 30.03 diabetics among the 272 siblings transferred now to the *Mm* × *mm* class. Our expectation of diabetics would then be increased by 30.03 − 11.84 = 18.20 individuals; so that instead of expecting approximately 98 diabetics in the total population (Tables 4 and 5) we would expect 98 + 18 = 116. The probable error for such an expectation would be approximately ±6.64 individuals, so that the deficiency of 20 siblings engendered by the increased expectation would be barely significant. If this increased expectation were to be met exactly then we would expect that 20 of the 1698 siblings classed as non-diabetic were really diabetic but had been overlooked as a consequence of the defects of the method of obtaining family histories.

Now it happens that the median age of these parents is a little over 65 years. At this age a little over 50 per cent of the potential diabetics are identifiable as diabetics (see Table 3, columns 5, 8 and 11). Therefore our 80 diabetic parents may, on certain grounds, be taken as slightly more than ½ the number of real diabetics, *i. e.*, *mm* individuals. Accordingly the illustration just given might very well apply except that a small proportion of the potential diabetics would be taken as mated to *mm* individuals already identified, *i. e.*, known diabetic parents, and the expectation of diabetes among the offspring would thereby be somewhat further increased.*

There can be, of course, no doubt that the proportions of diabetics in the two types of cross are significantly different. In the matings listed as *Mm* × *Mm* the observed percentage of diabetics is 4.28,

* To illustrate the complexity of the problem of deciding the proportion of the *mm* parents unidentified, the following two considerations may be mentioned. First, if, as seems not altogether unreasonable and is to some extent indicated in our data, there is a correlation between age of onset of diabetes in parents and in children, then, since we have chosen these families because at least 1 child is diabetic, the probability exists that an exceptionally large proportion of the parents capable of developing diabetes have developed the disease merely on the basis of the presumed parent-child correlation. Second, if we calculate the proportion of *Mm* to *mm* individuals in a Mendelian population breeding at random, then a general incidence of potential diabetics (*i. e.*, of *mm* individuals) of 4 per cent would require 88.9 *Mm* to 11.1 *mm*, or if the potential diabetics were equal to 3 per cent of the general population then the expected proportions would be 90.5 *Mm* to 9.5 *mm*. We actually have among these parents 91.9 non-diabetics to 8.1 diabetics. The maximum error in identification on this basis would be 27.03 per cent, indicating that at most some 22 *mm* parents are unidentified. This, of course, would make no significant alteration in the expected ratios among the children. But we are not at all certain that these parents are the result of random mating; nor are we certain of the general incidences of potential diabetics though crude estimates approximate those employed in this illustration.

and in the *Mm* × *mm* matings the observed percentage is 10.70. Since the median age of the siblings in the two groups is approximately the same, 42 years in the *Mm* × *Mm* group and 45 years in the *Mm* × *mm* group, the two crosses are crudely comparable on the basis of their percentage probable errors. The probable errors for the observed ratios among the siblings in the two crosses are respectively 0.35 per cent and 1.21 per cent, and the probable error of the difference is 1.25 per cent. The actual difference is 6.42 per cent which is 5.14 times the probable error of the difference, indicating a statistically significant difference between the 2 groups. Furthermore, if our classification of these matings is correct, and the age-distribution of the siblings roughly comparable, we should expect the percentage of diabetic siblings in the *Mm* × *Mm* group to be about ½ the percentage of diabetic siblings in the *Mm* × *mm* group. If we calculate the expectation among the siblings on the basis of the average of 3.40 children *per* family in the *Mm* × *Mm* cross and 3.69 children *per* family in the cross *Mm* × *mm*, the crude ratio of the expectations is 1:2.17. Or if we employ the approximate expectations of our tables (4.35 per cent to 11.04 per cent) the ratio is 1:2.54. The observed percentages, 4.28 per cent in *Mm* × *Mm* and 10.70 in *Mm* × *mm*, are in ratio 1 to 2.50, and this is well within the margin of error. This may be taken to indicate that our classification of the crosses meets the Mendelian assumptions.

Further speculation is deemed fruitless, however, since the plain fact of the matter is that we do not know enough about the family history of the parents to enable us to calculate with any exactness the proportion of *mm* individuals among them. All that can be said is that on purely genetic grounds there is probably a greater deficiency of diabetic siblings than our tables (4 and 5) make apparent, but that this deficiency may be made up for by the fact that there exist a number of cases of diabetes among these siblings that our method of collecting the family histories failed to reveal.

The obvious moral to this situation is that the direct examination of every member of a diabetic family might very well obviate a number of pitfalls and uncertainties. This is, in fact, what we propose to do. In succeeding papers we shall present the statistics resulting from such examinations. It has been deemed advisable, however, to put on record the results of this inquiry into the family histories, and to reëxamine these data and all that accrue subsequently, in the light of the results obtained from the direct examination.

That diabetes mellitus may be inherited has, of course, long been entertained as a possibility by numerous investigators (for references to the earlier literature see Baur, Fischer, and Lenz,[3] Cammidge,[6] Finke,[7] Joslin,[8] Kennedy,[9] White,[1] and Wright[10]). The presentation of family statistics has generally been of two types: (1) The listing

of genealogies in diabetic families (see von Noorden,[11] Buchanan,[12] Hansen,[13] Holst,[14] Strange,[15] Landsberg,[16] Cammidge,[6] Finke,[7] J. S. Wright,[10] *et al.*); (2) the listing of diabetes incidence among relatives of diabetics with little statistical analysis of the significance of these incidences (for examples, see Joslin,[8] Finke,[7] Høst,[17] also John,[18,19] Wendt and Peck[20]). In none of the papers that have come to our notice have any direct attempts been made to ascertain the possible Mendelian basis of the disease. The statement has indeed been made by Buchanan[12] that diabetes incidences in 34 diabetic families examined by him do not support a Mendelian hypothesis, but he does not give details of his analysis, and the data of the genealogies that are figured in his paper as far as they go do support an hypothesis of recessiveness. The casual inspection of a genealogy, and the consequent observation of a deficiency of diabetics on ordinary Mendelian assumptions does not necessarily vitiate these assumptions, since a number of siblings or parents may either be too young to develop the disease or die before they have the chance to develop it. This has been very properly pointed out by Finke,[7] and his data illustrate the point, though not *in extenso*. An ideal genealogy would be that of a family in which every member of the family had lived beyond the 9th decade, so that complete opportunity for expression of the disease were given to every member of the family. Even then one need not necessarily expect the calculated Mendelian ratios to obtain if the possibility exists that certain individuals who are potential diabetics never develop ascertainable symptoms of the disease. We have ignored this possibility in the treatment of our data, because it is unnecessary. What we have demonstrated is that the potentiality for developing diabetes behaves in these families *as if* it were a Mendelian recessive. We might conceivably be dealing with a dominant gene the expression of which is suppressed or not possible in a certain proportion of the cases, but this in no way detracts from the present analysis nor the practical consequences of it. Ideally we should have some specific test of latency that would obviate calculations based on age incidence.

Most investigators have been wary of accepting Mendelian interpretations, and very properly so. Their data are not of the sort that would enable a forthright decision. Any statistical analysis must depend on a knowledge of the ages of the non-diabetic as well as the diabetic members of the families examined, and if possible a knowledge of the family histories of the parents as well as the children. But it may be pointed out that if heredity is accepted as a factor in the etiology of the disease then this heredity must presumably be Mendelian. The known cases of non-Mendelian inheritance (*e. g.*, maternal inheritance of plastid characters in plants) are rare and rather special. The specific decision to be made is whether we are dealing with the expression of a dominant

or recessive gene or genes. Obviously one must choose the simplest explanation, and in the case of diabetes mellitus our data as far as they go support the notion of the inheritance of a single recessive gene.

Summary. The incidences of diabetes are significantly higher in families of diabetic patients than in families of non-diabetic patients. If we accept the assumption that potential diabetics before they develop the disease have the same expectations of life as persons generally, it can be demonstrated that the observed occurrence of diabetes in the children of the diabetic families is in accord with the hypothesis that potentiality for developing diabetes is inherited as a simple Mendelian recessive. The probability that certain parents classed as non-diabetic are genetically diabetic would indicate that there is, on our hypothesis, a deficieney of diabetic children in these diabetic families, but this presumed deficiency may be due to the limitations of the method of collecting family histories. In any event the data behave as if our identification of diabetics among the parents and children were in accord with Mendelian expectations, provided our calculations of the relative number of potential diabetics present in each decade are correct.

We wish to acknowledge the kind coöperation and advice rendered to us by Dr. E. P. Joslin and Dr. W. J. Crozier; and to Dr. E. B. Wilson we are indebted for his discussion and criticism of the analysis. Material assistance was also received from a fund created by Mr. and Mrs. Francis P. Garvan.

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THE METABOLISM OF LEVULOSE.*

I. SOME GENERAL CONSIDERATIONS ON PROVOCATIVE LEVULOSURIA.

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DURING the past 10 years the senior author and his associates have published a series of papers[77] embodying the results of extended investigations on the metabolism of galactose in man. Briefly summarized, these studies have shown that this sugar exhibits an interesting sex difference in the capacity for utilization which is tentatively ascribed, in part at least, to the specialized mammary mechanism of the female. Further, these studies have demonstrated that a wide variety of physiologic and pathologic conditions severally influence the tolerance levels in characteristic ways.

A survey of the fairly extensive literature on the metabolism of another hexose, levulose, discloses a series of seemingly significant differences in behavior from that shown by galactose in the same conditions. Obviously, these differences, if they could be confirmed, might throw more light on the complex interrelationships of our carbohydrate metabolism and equally could assume a differential meaning in some of the disease states with which they were associated.

Influenced by these considerations, studies have been undertaken, duplicating with levulose those already completed with galactose. The present paper is the first and preliminary report and embodies certain of the general considerations together with a few illustrative results from those already obtained.

Nearly 50 years ago, Hofmeister[47] studied the assimilation and utilization limits for a number of individual sugars, feeding them in graded dosage to fasting subjects and observing the level at which the sugar first appeared in the urine. This technique, with a variety of minor modifications, remained the basis of sugar tolerance testing until the development by Folin[24] and others of reasonably accurate microchemical methods for the quantitation of blood sugar turned attention to this method of approach. While the earlier

* Presented at the Forty-fourth Meeting of the American Physiological Society, Philadelphia, April, 1932.

blood sugar studies defined a series of curves which were regarded as characteristic of individual pathologic states,[29,69] later investigations[2,20,76,93] have cast grave doubt on the specific nature of these curves, have shown that other mechanisms are involved, and have sharply delimited the quantitative aspect of the method. In spite of these facts, blood sugar curves obtained by straight line interpolation between isolated points determined at conventional time intervals after a provocative test meal of glucose (100 gm. or 1.75 gm. per kilo of body weight[57]), still remain the method of election of a large number of observers.

In 1899, Sachs[83] reported the interesting observation that dehepatized frogs showed a depressed tolerance for levulose but not for glucose or galactose. Two years later, Strauss[90] utilized this suggestion to develop a test for liver function with this sugar, and in subsequent papers[91,92] reaffirmed its distinctive and differential character. In the supervening years a number of other investigators have applied the test, using either the urine or blood indications or both with reported results that are highly contradictory. While one group of observers[8,13,19,26,30,40,85] for a variety of reasons find the levulose tolerance to be worthless as an index of disturbed liver function, Rebaudi[73] and many others[18,27,32,55,81,82,91,92] report it to be a delicate indicator of certain types of hepatic derangement. Clinical reports of studies on groups of hepatopathics range from a 100 per cent positive response with 100 gm. of sugar[18,81,82,91] to a 30 per cent indication under the same conditions.[43,48] Several writers stress the point that the type of liver condition is an important factor in determining the response to levulose, since the relative amount of surviving functioning tissue may cause wide variation.[50] This serves both to explain certain of the discrepancies in recorded results and equally to offer information of possible differential value.

The recognition of departures from the normal presupposes the establishment of normal criteria; but here again wide fluctuations are reported, ranging from groups in which no case showed levulosuria after the ingestion of 100 gm. of sugar,[82,91] to one series in which 57 per cent yielded positive urines after this test meal.[64] In another series 9 per cent were positive after 60 gm.,[1] while in yet another, 50 gm. gave an uniformly negative response.[55] Unfortunately, a large part of the measurements were made upon so-called "hospital normals," a fact which both invalidates the indications and offers a possible explanation for the discrepancies in the several reports. Goetsch, Cushing and Jacobson[31] regard 100 gm. as the probable tolerance normal; v. Noorden[68] placed it as between 1.7 to 2.1 gm. per kilo of body weight.

On the basis of the urine findings, the tolerance is reported as depressed in syphilis,[5,28] nephritis,[17,27] tuberculosis,[17] polycythemia,[28] and epilepsy;[33] and normal in leukemia,[5] cancer,[11,43,50] primary ane-

mia,[59] gastric ulcer,[55] and cystic ovaries,[32] to name some among the many. There is a general downward tendency in pregnancy, although individual series show variations between 60 per cent[34] and 100 per cent.[46,74] The worthlessness of the uncontrolled carbohydrate tolerance as a test for pregnancy has been too conclusively established to require comment here. Aberrations in the endocrinopathies are also reported (V.I.).

Whereas, a test meal of glucose—and in lesser degree galactose—will produce a significant rise in blood sugar, levulose exercises but slight influence on the observed levels in health. It is usually conceded to be abnormally high in liver cases,[7,15,19,44,61,70,89,94,97] although occasional qualifying limitations are recorded.[22,37,39,45] There is a definite lack of agreement, however, as to the line of demarcation between normal and abnormal increase, the range being from 4 mg. with 60 gm.[67] and 8 mg. with 45 gm.,[61] through 20 mg.[34,44] with 100 gm. to 30 mg. with 45[19,94] and 36 mg. with a test meal of 100 gm.[53] The liver indices are usually given as more than 20 mg. with doses of from 30 to 50 gm.,[37] or that blood sugars following a test meal are indicative of hepatic dysfunction if they exceed from 125 mg.[58] to 135 mg.[37] Another criterion of liver involvement is a sharp rise and slow decline to the curve,[44] while a maximum at 34 to 37 minutes is regarded as normal.[66] Curves in pregnancy are recorded alike as normal[16] and abnormal.[46,60,67] Blood sugar levels indicate decreased tolerance in syphilis,[39] amebiasis,[15] rheumatic heart,[10,12] cancer of the pancreas,[37] chorea,[12] psychosis,[84] and malaria,[97] and are normal in ketosis,[9] sprue,[15] primary anemia,[38] pneumonia,[97] paralysis agitans,[52] and following abortion.[35] Endocrine influences have also been studied.

These reports serve once more to emphasize the lack of value of the response of the "hospital normal" as the basis for the establishment of normal criteria. Further, it will be patent from the above brief review that the changes in blood sugar levels produced by test meals of levulose are even less well adapted than those obtained with glucose to indicate moderate divergences from normal function. Only incidental reference will be made to blood sugars in the remainder of this communication, as the topic will be treated in detail in a later paper. The present reports are based upon the urine findings following a modified Hofmeister[47] technique.

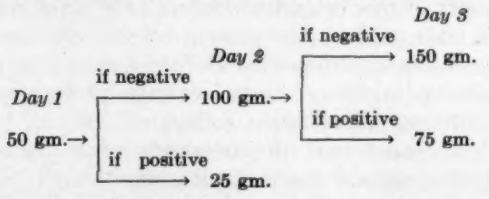
In determining tolerance limits, certain precautions must be taken if disturbing physiologic influences are to be excluded. Traugott[95] has emphasized the necessity of a preliminary diet control to insure normal tissue saturation, though Soisalo[88] feels this to be unnecessary, if blood sugar levels are the criterion. Fasting decreases tolerance,[75] exercise produces an opposite effect,[4,49] unusual environmental temperatures may change the tolerance level.[51,70]

The purity of the test sugar is of vital importance, particularly

if the urine findings are the indicator. Kraus and Ludwig,[62] in 1891, found that 100 gm. of commercial glucose would produce melituria, while double that amount of a purified product yielded only negative results. Several later studies have substantiated this conclusion,[23,96] and in the first paper Folin and Berglund[23] have emphasized the necessity of excluding from the test meal all reducing bodies which are capable of assimilation but not of utilization. The use of a sugar containing menstruum in which to administer the test meal,[12,30,41,50] such as milk or natural fruit juices, should be wholly interdicted. Passing comment may be made on the proposal to use a mixture of sugars for the test meal;[11,-21,36,85] the procedure has nothing to recommend it and can readily lead to erroneous conclusions. With levulose, the need for purity becomes even more insistent, for reasons other than those already given. In most of the levulose now obtainable there is present an impurity which exercises a powerful laxative action on the gastro-intestinal tract. Folin and Berglund[23] record disturbing experiences with levulose which had been autoclaved. We have had it uniformly with sugars from several sources which lacked final purification. Seemingly the substance can be eliminated by repeated recrystallizations from alcohol, but the product thus prepared is very expensive. Recent experience holds out the hope that a sugar can be prepared from the Jerusalem artichoke, at about one-fourth the cost of the other product, which is free from this disturbing substance. In the present studies only purified material has been used,* as diarrhea completely destroys the authority of the quantitative approach. It seems probable that some, at least, of the discrepancies in the previously reported assimilation limits of levulose may be ascribed to varying amounts of impurities in the several sugars used.

The general method of administering the graded doses of levulose followed that adopted originally for galactose, the higher tolerance of the former sugar determining larger individual doses. The plan can best be shown in the accompanying graph.

GRAPH I.—SCHEME FOR ADMINISTRATION OF LEVULOSE.



As the work has progressed, it has been possible to modify the program as presented to meet the needs of the individual case. As

* We are indebted to the Pfanstiehl Chemical Company (formerly the "Special Chemicals Company") of Waukegan, Ill., for a generous coöperation in the laborious purification of this material.

experience shows a definite upward or downward trend in a given condition, the initial dose may be selected accordingly and the test performed with a saving of time, money, and the patient's convenience. The technique of administration of the individual dose is given in Table 1:

TABLE 1.—DIRECTIONS FOR LEVULOSE TEST.

On the day of the test the following outline is to be observed:

1. At 5 A.M. void urine and discard.
2. At 7 A.M. void urine which has been gathering during the last 2 hours and save. This is Urine No. 1.
3. As soon as the urine has been voided, take the dose of sugar as sent, which you have dissolved in about 6 to 8 ounces of water (½ pint), drinking all of it. (Use more water with larger doses.)
4. At 9 A.M. collect the urine which has been gathering between 7 and 9. This is Urine No. 2.
5. At 11 A.M. collect the urine which has been gathering between 9 and 11. This is Urine No. 3.

IMPORTANT.

No food other than sugar is to be taken until 11 in the morning, at which time breakfast may be eaten. Water may be drunk reasonably. It is desirable that the patient remain in bed until breakfast.

Each urine should be placed in a separate container and carefully marked with the proper number. The name of the patient should be marked on the wrapped parcel. The entire collection should be sent to this laboratory as soon as completed, that is to say, in the afternoon of the day on which the test is made.

In the selection of cases for study, it was recognized that not only should the primary diagnosis be definitely established, but that complicating conditions, the presence of which could influence the tolerance level, must be equally carefully evaluated. To this end, each case studied was either given the full diagnostic procedure ("Long Form") described by one of us,[78] or its equivalent for those patients who could not be hospitalized for the entire period of study. The normal controls were given the morning study ("Short Form") described in the paper already cited,[78] such special tests as were indicated for the individual subject, and both the galactose and levulose tolerance determined as already described.

The urines were tested qualitatively with the well-known Benedict reagent[6] and by the Seliwanoff[87] method. The quantitative measurements involved the Folin-Berglund procedure[25,72] corrected for the levulose coefficient and the polariscope, clearing the urine with Lloyd's reagent, and applying the correction for the slight levorotation of normal urine as reported by Haas.[42] Bulky urine samples were tested qualitatively and, if negative, concentrated and retested. This possibly disturbing factor can be readily controlled by reasonable regulation of the water intake during the test period. The full details of the analytical procedures for both urine and blood will be embodied in a subsequent paper. The methods used were selected after careful comparative study of existing procedures.

As stated earlier, the present paper is a preliminary communication and the data reported are illustrative of certain aspects of the study. The definition of normal standards of tolerance is the primary desideratum, as only by their establishment can departures be recognized and interpreted in terms of aberrant carbohydrate metabolism.

Control Group "A," the general data of which are given in the next table, was composed of 7 young women completing their third year of study in the Sargent School of Boston University who volunteered for this phase of the investigation.*

TABLE 2.—DESCRIPTIVE DATA.

Control Group "A" (Female).

Subject—	Ba.	De.	Fo.	Gr.	Ki.	Le.	Ro.
Age	20	20	21	20	20	20	22
Weight (deviation)	−5%	+1%	−2%	±0%	+3%	+40%	−7%
Lung volume deviation†	+6%	+13%	+2%	+7%	+16%	+8%	+4%
Urine	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Total nitrogen (gm.)	7.74	9.13	...	7.49	12.49	7.88	7.23
Blood chemistry	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Blood morphology	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.
Basal rate (deviation)	−10%	−6%	−6%	−11%	−6%	−2%	−5%
Blood pressure (mm.)	110/60	100/58	110/70	106/60	118/68	114/82	112/66
Pulse	72	62	70	60	68	64	72
Temperature (° F.)	98.2	98.2	98.2	98.0	98.2	98.6	98.2
Alveolar CO_2 (mm.)	43	46	44	46	46	44	43
Galactose tolerance (gm.)	40	40	40	40	40	40	40

Carefully compiled medical histories gave no evidence of significant abnormality and the physical examinations were completely negative. We should like to stress at this point the necessity of such careful surveys to assure the normality of the "normal" control. All of these young women were in robust health and carrying successfully a full college program which, from the nature of the school, involved a daily quotum of active physical exercise. The one subject who was significantly overweight (Le) had a somewhat low sitting height index (0.516) which tends to exaggerate her departure from prediction. She was a large-framed powerful girl and the overweight seemingly no more than a personal characteristic. Two of the basal rates were low borderline values. This work was done in the spring, as the college year was approaching its end, and the senior author has frequently remarked a slight downward tendency to the respiratory metabolism of college groups at this season of the year. The results of the sugar tests with this group are collected in Table 3.

* The authors express their deep appreciation for this gracious coöperation.

† This term was adopted a number of years ago instead of the meaningless form "vital capacity." Perhaps "respiratory capacity" could still better be used to indicate this measurement, which is not to be regarded as vital.

TABLE 3.—SUGAR TOLERANCE.

Control Group "A" (Female). (All figures are in grams.)

Subject:	Ba.	De.	Fo.	Gr.	Ki.	Le.	Ro.
Galactose:							
30 gm.	0	0	0	0	0	0	0
40 gm.	0.75	1.11	0.43	0.61	1.01	0.54	0.36
Levulose:							
75 gm.	0	0	0	0	0	0	0
100 gm.	0.16	0.11	0.16	0.13	0.12	0.14	0.13
125 gm.	0.20	0.31	0.22	..	0.19	..	0.23

All of the girls were positive with 40 gm. of galactose and negative with 30 gm., using the criterion as designated in the earlier galactose papers[77] of qualitative response to Benedict's reagent. With the levulose, both the Benedict test and that of Seliwanov were applied and where positive response was secured the amount of levulose was estimated quantitatively. All responded positively to the 100 gm. test meal, the amounts eliminated showing a surprising uniformity. The slight increase in the amount eliminated with the larger dose of 125 gm. is an interesting illustration of Allen's[3] "carbohydrate paradox." The complete uniformity of the response of this group is fortuitous. The tolerance level indicated, however, is certainly not far from that which a larger series will define.

The volumes of the test urines varied from 65 to 195 cc. and showed no regularity in relation to the sugar content. Seemingly the water drunk during the collection period of 4 hours is the determining factor. Janney's[56] recent figures on forced water elimination are possibly significant in this connection. With the present group no effort was made to control water intake.

As Strauss' work on liver function may be said to be the starting point of provocative levulosuria studies, a few figures on the influence of hepatic dysfunction may next be considered. The significant data from a few cases are collected in the next table. It should be said in passing that the hepatic element in each case was established by careful clinical and laboratory studies, the details of which will be given elsewhere.

TABLE 4.—HEPATIC DYSFUNCTION, UNCOMPLICATED.

Sex.	No. of cases.	Galactose tolerance. Response.	Galactose tolerance. Deviation (%).	Levulose tolerance, average dose, gm.
Male	2	Normal	±0	63
Male	3	Depressed	−56	67
Female	9	Depressed	−61	53
Female	2	Depressed	−38	100
Female	4	Depressed	−50	156

The ages in this group ranged from 13 to 71 years with an average of 37 years. A partial review of the literature yields a group of 954 cases of liver dysfunction of highly diversified characters of whom 649 (68 per cent) gave a positive response to 100 gm. of

levulose. In one small group of 8 cases,[5] 5 (63 per cent) were positive with 50 gm., while another author[55] reports 33 in 43 (77 per cent) positive with the same test meal. On the other hand, Friedman and Strouse[30] report a number of liver cases giving a negative response to 90 gm. of levulose administered in lemonade(!), and another investigation[63] reports a variety of hepatic conditions which responded uniformly in the negative to a test meal of 40 gm.

Our own figures show a considerable degree of variation, although 80 per cent give a positive response to 100 gm. or less. Interesting is the group of 4 women, all with depressed galactose tolerance, whose average response of 156 gm. suggests, at least, an increased tolerance. The senior author has already reported a like anomaly with galactose in liver cases.[77h] The lack of quantitative correlation between the galactose and levulose results suggests once more the probability that the mechanism of utilization of the two sugars is probably not identical.

Lowered functional activity of the thyroid, where it affects sugar tolerance, determines an upward trend of modest proportions. In a long series of uncomplicated cases of hypothyroidism[65] the senior author, with galactose, has found two-thirds to be normal, the remainder demonstrating an average increase of some 30 per cent above prediction. In a paper recently presented,[80] one of us (A.W.R.) has pointed out the frequent association of hepatic dysfunction with lowered thyroid activity. In such cases, as might be anticipated, there is an usual depression of the carbohydrate metabolism, which is the expression of the algebraic summation of two opposite—and usually unequal—forces. In the next table are collected results from a small group of thyroid cases, a portion of which shows the liver complication.

TABLE 5.—THYROID FAILURE WITH (A) AND WITHOUT (B) HEPATIC COMPLICATION.

Group.	No. of cases.	Galactose tolerance.		Levulose tolerance, average dose, gm.
		Response.	Deviation (%).	
Thyroid alone:				
A	6	Normal	±0	71
B	1	Increased	+25	Over 175
Thyroid-liver				
A	5	Depressed	−35	80
B	2	Depressed	−25	150

The galactose tolerances of the uncomplicated thyroid cases are in harmony with previous experience, the majority showing a normal value, and the exception an increase of modest proportions. The average for the levulose response of Group "A" is definitely below the 100 gm. level, which has been the criterion of many of the earlier observers while, equally, the single case with slightly increased galactose tolerance was negative with the somewhat massive dose of 175 gm. of levulose. Parallel records in the literature are few in number. In a paper previously cited,[30] the authors

administered 90 gm. of levulose dissolved in lemonade with the following results:

Three cases of hypothyroidism were negative, 9 in a group of 18 hyperthyroid cases were negative, and 5 cases of simple goiter were all negative. The authors note some uncertainty in the diagnoses as offered.

The group with hepatic complication parallels the record of the uncomplicated liver group, in quality at least. The figures are possibly suggestive; the limited number of cases argues for caution in interpretation.

The presence of an hepatic factor in many cases of toxic pregnancy renders data from this source apposite to the present discussion. A number of records from another investigation has been collected in the next table. Others, from a short series of normal pregnant women, are included as a rough control.

TABLE 6.—TOXIC AND NORMAL PREGNANCY.

Group.	No. of cases.	Months, average ante-partum.	Tolerance.	
			Galactose.	Levulose (av., gm.).
Toxic A	4	4+	Depressed	44
B	13	2+	Normal	56
C	3	1+	Increased	75
Normal	9	3	Normal	72

At first sight there would seem to be some systematic relationship in the response to the two sugars, as with a rising galactose tolerance the relative capacity for assimilating levulose also increases. This seems to be a dependable datum. Although not all of these cases had a proven hepatic factor, the actual status of each case seemingly affects both sugars alike, at least in direction if not in amount. The same cannot be said for the apparent interdependence of the sugar on the time interval before delivery. The values are averages and the cases in the divergent groups are too few in number to give a final authority. That a trend is suggested may be conceded, however. The levulose figures for normal pregnancy are practically the same as for the toxic group with increased galactose tolerance.

In a series of 217 cases of presumed normal pregnancy drawn from a number of sources in the literature, 180 (83 per cent) were positive with the single test meal of 100 gm. of levulose. Van Creveld and Ladenius,[16] in a series of 60 pregnant women, 53 of whom were in the first 3 months, found that 38 per cent were definitely positive and 9 more vaguely so with test meals of from 40 to 60 gm. of this sugar. On the other hand, Schroeder[86] found only 17 of 95 cases of pregnancy to be positive with 150 gm., and of this group only 3 gave a strong reaction in the urine.

The possible influence of pregnancy on the level of endocrine function of the ovaries[79] warrants survey of the results obtained

with groups in which ovarian function presents characteristic levels. These data are given in Table 7.

TABLE 7.—OVARIAN INFLUENCE.

Status.	Duration.	No. of cases.	Tolerance (average). Galactose (gm.).	Levulose (gm.).
Normal, prepuberty	....	9	20	75
Normal, adult	....	15	40	108
Hypofunction	Years	4	20	75
Castration	Weeks	2	30	75
	"	1	20	75
	"	1	10	125
Castration	Years	3	20	125

Analysis of these figures presents some puzzling problems. The prepuberty child has a low galactose tolerance and responds uniformly to 75 gm. of levulose, while the tests with 50 gm. were equally negative. In adult years the galactose level doubles, but the levulose, while it follows the same directional trend, shows a very modest increase. Ovarian hypofunction produces a consistent lowering with both sugars, but in established castrates, though the galactose demonstrates the significant lowering to prepuberal levels elsewhere reported,[77d] the levulose response is at a level superior to the average value for the intact adult. Three of the 4 early castrates show a levulose response consistent with that of galactose. The fourth, on the other hand, shows too low a galactose and too high a levulose to be harmonious with the other data. A possible injury to the central nervous system, disclosed by the complete study of the patient, would account for the abnormal galactose level, but raises a new question in regard to the levulose metabolism. But little added information may be derived from the literature. Coppioli[14] reports a lowered tolerance in aged women and there are a few animal experiments which equate but ill with studies in man.

While, as stated initially, the results here presented are in the nature of illustrations to some of the general considerations, the implications of the data presented may be briefly discussed.

Discussion. It would seem probable that there is a fairly well defined zone for normal individuals within the limits of which doses of levulose will commonly produce transitory levulosuria when the sugar is administered with due regard to certain standardizing conventions. Among these should be named a preliminary establishment of reasonable tissue saturation, the administration of a very pure sugar without admixture of uncertain amounts of foreign sugars, the application of the test to subjects in an initial basal condition, and the avoidance of exercise and exposure to extremes of temperature during the test. Levulose shows a definitely higher level of utilization than does galactose, the ratio being apparently of the order of about 3± to 1. In general, conditions producing fluctuations in the galactose tolerance engender like changes in

that of levulose which are usually similar in direction but not in amount. Hepatic dysfunction of various types affects the utilization of both sugars. The anomalous increase in tolerance already observed with galactose seemingly finds more frequent expression when levulose is ingested. The influences of some of the function levels of individual endocrine glands on galactose utilization are not always directly reflected with that of levulose. Jacobson[54] had already noted differences in the behavior of glucose and levulose in hypophysectomized dogs with Eck fistulæ.

In other words, preliminary study of the levulose tolerance in a series of small groups of selected cases demonstrates these differences from the behavior of galactose in the same conditions that were broadly suggested by a review of the literature. The verification and definition of these and other differences and similarities will be treated in later papers.

Summary. A brief review of some of the existing literature on levulose tolerance has been made and the numerous contradictions found therein noted.

A standard technique based on the Hofmeister procedure for the determination of the tolerance has been outlined. The necessity for the use of very pure sugar and certain other limiting conditions have been emphasized.

A series of comparative studies on selected groups has been carried out with both galactose and levulose. Observed coincidences and discrepancies are recorded and lead to the conclusion that there are real differences in the mechanism of utilization of the two sugars.

NOTE.—The authors wish to express their indebtedness to the members of the Evans staff who coöperated in the diagnostic procedures and to the subjects of these investigations who cheerfully made the sacrifices necessary for the performance of these studies.

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THE INCIDENCE AND SEVERITY OF ARTERIOSCLEROSIS IN THE ORGANS FROM FIVE HUNDRED AUTOPSIES.*

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A common diagnosis made in the clinic and at the autopsy table is that of "generalized arteriosclerosis." Often it is the only diagnosis; more frequently it is used to explain such complexes as "essential hypertension," or "cardio-renal vascular disease." The clinician discovers that his patient has hypertension, finds the peripheral arteries hard, tortuous and supposedly sclerotic, elicits, perhaps, signs of myocardial degeneration or of disturbed kidney function, and consciously or unconsciously he thinks of them in terms of a widespread arteriosclerotic process. The pathologist, on the other hand, may encounter difficulties when he attempts to correlate the clinical with the pathologic findings. Often the most careful examination fails to show a generalized sclerosis of the vascular system in the literal sense of the term. The vessels of some organs are

* Read before the Pathological Society of Philadelphia, January 12, 1933.

affected to a marked degree, those of others not at all or only slightly, and frequently the vascular tree of a particular organ is not uniformly involved.

With these and related facts in mind the present study of 500 autopsied cases was undertaken to determine the incidence, distribution and degree of arteriosclerosis in the various organs of the body.

Review of Literature. As the literature on the distribution of arteriosclerosis is meager and widely scattered, a short résumé may be of value. Dow,[1] using as criteria the degree of hardness and thickness of the arterial walls of 8 cadavers in the dissecting room, found that the abdominal aorta, femoral and popliteal arteries were most frequently and most extensively affected, whereas the mesenteric arteries were strikingly seldom the seat of degeneration. In the pelvis the internal iliacs and the parietal vessels were more often involved than the external iliacs or the visceral vessels. The arteries of the lower extremities were more commonly sclerotic than those of the upper. The arteries which supply the cerebrum were of especial interest: that portion of the internal carotid artery which lay in the cavernous sinus, particularly the bifurcation into the anterior and middle cerebral arteries, frequently presented sclerosis of a very advanced degree. This was in marked contrast to the cervical portion of the internal carotid, which seldom showed degeneration. The tricuspid valve and the pulmonary artery were not implicated in any case, but the mitral valve and the thoracic aorta were often the sites of sclerotic processes.

Brooks[2] studied the incidence of visceral arteriosclerosis as revealed by gross examination, utilizing only those cases in which arterial changes were of a sufficiently pronounced character to influence obviously the clinical as well as the anatomic manifestations. His results represent, therefore, large vessel sclerosis. The order of frequency of involvement in 368 cases was as follows: aorta (333 cases), coronary vessels (270), brain vessels (132), renal vessels (81, all with marked involvement), pancreas (74), hepatic vessels (43), splenic vessels (35), lungs (11), coeliac axis and its visceral branches (19) with a diffuse involvement of the mesenteric vessels in 4 cases, and the spinal vessels in 20.

Norris and Landis,[3] quoting Rokitansky, state that the frequency with which the different parts of the arterial tree are most affected is: aorta (arch, descending and abdominal portions), iliacs, crurals, coronary arteries and cerebral arteries. They emphasize that arteriosclerosis may be selective and unequally distributed throughout the body: "The pipestem radials of the day laborer are often associated with fairly good visceral arteries and in such cases constitute a benign form not at all incompatible with long life."[3]

The incidence of sclerosis in the arterioles and small arteries has been investigated by a number of workers. Jores[4] found changes most frequently in the arterioles of the kidney, spleen and pia mater;

less frequently in those of the stomach, intestines and liver. The coronary vessels were unique in that the arterioles were always free from involvement even when the larger branches were markedly diseased. Fahr[5] and Herxheimer[6] confirmed the findings of Jores. Fahr reported that of 44 cases of hypertension the small arteries of the pancreas were involved in 38 of them. He especially noted that the gastro-intestinal tract was rarely implicated. Herxheimer stated that arteriosclerosis of the spleen occurred with increasing frequency from early youth to old age and was present in a majority of elderly patients, apparently without relation to hypertension.

Studying arteriosclerosis in relation to renal disease, Evans[7] found that a diffuse hypoplastic sclerosis was most common in the kidney. It was not found in other organs unless also present in the kidney and spleen, where the lesions were always more marked. In its typical development this form of arteriosclerosis is not encountered in the heart, lung or skeletal muscle.

Evans[8] also studied the incidence of arteriosclerosis in 4 children. He writes, "The incidence of the lesion (arteriosclerosis) in the various organs follows that found in adults in its main features, that is to say, the kidney and spleen are most affected, the pancreas and suprarenals are next in order, the affection of the intimate vasculature of the liver is slight and the heart escapes. It is noted that the vessels in the brain were not affected in these cases, whereas those in the stomach were." In these two respects the incidence of the lesion is different from that in adults.

Fishberg[9] states that in 72 cases of essential hypertension which came to necropsy, lesions of the terminal arterioles were invariably present. In all his cases the arterioles of the kidney were involved. The splenic arterioles were affected in two-thirds of the cases, the pancreatic in one-half and the cerebral in one-fifth, but the lesions even when present in these organs were not as marked as those in the kidney. The myocardium, lungs, gastro-intestinal tract and thyroid were rarely implicated and then only to a minor degree. The author stresses the point that the distribution of arteriolarsclerosis differs from that of "large vessel atherosclerosis." The latter has its site of predilection in the heart, brain and extremities, while arteriolarsclerosis is most frequent in the kidney, spleen and pancreas. Bell and Clawson,[10] although they did not analyze their hypertensive cases statistically, nevertheless were of the opinion that Fishberg's results expressed the true distribution of visceral arteriosclerosis.

The incidence of arteriolarsclerosis in cases of hypertension was found by Bordley and Baker[11] in 23 cases to be as follows: Kidney 95.8 per cent, adrenals 79.2, pancreas 70.7, brain 58.3, heart 50.0, liver 25.0, and lung 16.0. Unfortunately no data for the spleen are given, but otherwise the results agree with those of the foregoing authors. Branch and Linder[12] found arteriolarsclerosis most frequently in the kidney, spleen and pancreas in the order given.

Klemperer and Otani[13] in a study of malignant nephrosclerosis reported visceral arteriolarsclerosis in every case. The pancreas, liver and adrenal were involved in about the same percentage as in simple hypertension. In addition they found arteriolarsclerosis in all the kidneys examined. The spleen was excepted on the basis of the extreme frequency with which arteriolar hyalinization was found in this organ.

Arteriolarsclerosis of the vessels supplying the voluntary muscles is thought by most workers to occur rarely. Watanabi,[14] in an extensive investigation of 116 cases of so-called generalized arteriosclerosis, found only 6 with involvement of the small arteries of the skin. Even when the lesion was widespread in many organs, Jores[4] and Fahr[5] were unable to demonstrate arteriolarsclerosis in skeletal muscle or skin. Branch and Linder[12] reported a similar condition in the arterioles of voluntary muscle. During the examination of 6 cases of nephrosclerosis, Klemperer and Otani[13] found no evidences of sclerotic lesions in the arterioles in either the abdominal muscles or the diaphragm. Evans[7] reports that diffuse hypoplastic sclerosis is not found in its typical development in the skeletal musculature. The terminal arterioles of the skin and voluntary muscles were found by Fishberg[9] to be rarely involved, and then only to an insignificant extent.

On the other hand, Kernohan and his colleagues[15] observed from biopsies on the voluntary muscles of ambulatory patients with diffuse, hypertensive, vascular disease, that the arteries often showed distinctive histologic changes. In those who later came to autopsy, lesions were found identical with the arteriolar lesion previously described at biopsy, as well as arteriosclerotic changes in many other organs. Kernohan's viewpoint is supported by the work of Sutton and Brandes,[16] who found that of 3040 autopsies performed at the Cook County Hospital 340 (11.1 per cent) showed gross arteriosclerosis and of this number 113 (32.2 per cent) had peripheral arteriosclerosis. Unfortunately the value of their work is diminished by the fact that the authors did not define their use of the term "peripheral arteriosclerosis." Recently Horine, Weiss and Beard[17] have reported a series of 11 patients who had "hypertensive heart disease without hypertension" (*sic*). Biopsies taken from the deltoid muscle revealed alterations in the intima and media of the arterioles similar to the changes described by Kernohan and his collaborators. The 1 case which came to necropsy disclosed a generalized arteriolarsclerosis.

Materials and Methods. The protocols and microscopic sections of 500 autopsies performed at the University and Philadelphia General Hospitals during 1925 were reviewed. While these autopsies were not consecutive, they were nevertheless unselected and hence may be regarded as representative of the pathologic services of two large hospitals. They possess the common feature that in all

cases sections were taken from both domes of the diaphragm. One has, therefore, in every case, the vessels of this skeletal muscle to compare with those of the various other organs. The postmortem records were searched for mention of gross arteriosclerosis, the following arteries being considered: The coronaries and the large arteries of the kidney and brain. In the microscopic sections the vessels examined were the small, unnamed branches of the visceral arteries and the arterioles. The degree of sclerosis was designated as being "mild" or "marked." In grading the sections two factors were kept in mind. First, the degree of involvement of the individual arteries and, second, the proportion of the total number of arteries affected in the particular sections studied, these being regarded as representative of the whole organ. The vascular changes classified as "mild" arteriosclerosis consisted of fatty changes in the intima varying from inconspicuous lesions to definite microscopic atheroma, and of a distinct thickening of the intima produced by the formation of new connective tissue. As "marked" arteriosclerosis were classified changes of a more advanced degree, such as greater thickening of the intima, hyalinization, fragmentation or reduplication of the internal elastica and involvement of the media.

TABLE 1.—THE INCIDENCE OF ARTERIOSCLEROSIS FROM GROSS EXAMINATION OF HEART, KIDNEY AND BRAIN.

Organ.	Number of cases.	Normal vessels (per cent).	Mild sclerosis (per cent).	Marked sclerosis (per cent).	Total sclerosis (per cent).
Heart	405	42.5	23.4	34.1	57.5
Kidney	442	44.2	20.0	36.0	56.0
Brain	90	20.0	17.8	62.3	80.1

TABLE 2.—THE INCIDENCE OF ARTERIOSCLEROSIS FROM MICROSCOPIC EXAMINATION.

Organ.	Number of cases.	Normal vessels (per cent).	Mild sclerosis (per cent).	Marked sclerosis (per cent).	Total sclerosis (per cent).
Heart	346	45.7	26.5	22.7	49.2
Lung	426	66.1	25.1	8.5	33.6
Spleen	426	10.9	24.4	64.9	89.3
Kidney	470	26.5	26.3	47.1	73.4
Liver	448	71.7	18.9	9.5	28.4
Pancreas	148	42.6	35.1	22.3	57.4
Brain	89	18.0	19.2	63.0	82.2
G. I. tract	70	57.9	27.9	14.3	42.2
Adrenal	75	38.7	29.4	32.0	61.4
Diaphragm	498	94.5	5.6	0.0	5.6

Results. The cases have been grouped into two tables (results of gross and microscopic examination) without reference to age, sex or race. In Table 1, the results of gross examination of the arteries of the organs at the autopsy table, only four organs are represented as the data concerning the others were insufficient. It indicates that the heart, kidney and brain were often implicated by an arteriosclerotic process of a degree sufficiently advanced to be recog-

nized grossly. In Table 2, the results of a microscopic examination of the arteries of the various organs, it is seen that the diaphragm, liver, lungs and gastro-intestinal tract had normal arteries in more than 50 per cent of the cases. Indeed, evidences of sclerosis were found in the diaphragmatic vessels in only 5.6 per cent of the 498 cases examined, and even this small percentage displayed but a mild involvement. The spleen, brain, kidney and adrenals exhibited, in the order named, the greatest incidence and the most marked degree of sclerosis.

A very interesting feature appears in Table 3, where the organs were arranged in the order of decreasing incidence of arteriosclerosis. It was found that those organs which were most often involved were also most markedly affected by an arteriosclerotic process. The arteries of the spleen, brain and kidney were sclerotic, for example, in 70 per cent or more of the cases and of these at least 60 per cent were involved to a marked degree. In the diaphragm, liver, lungs and other organs which are infrequently implicated, one noticed a high incidence of the milder forms of sclerosis and a low incidence of the more advanced forms. The diaphragm illustrated this point very well: of a total percentage of arteriosclerosis of 5.6, no case showed marked involvement. In the liver and lungs less than one-third of the sclerotic cases were involved to a marked degree; whereas 60 to 75 per cent of the same cases exhibited milder forms of the lesion. The heart, pancreas and adrenal showed an approximately equal incidence of mild and of marked arteriosclerosis. An important exception is the interesting fact that the brain, although it did not show the greatest total percentage of arteriosclerotic cases, did present the highest incidence of marked involvement.

TABLE 3.—ORGAN INCIDENCE OF MARKED VERSUS MILD ARTERIOSCLEROSIS.

Organ.	Total per cent of sclerosis.	Per cent of total sclerosis with marked sclerosis.	Per cent of total with mild sclerosis
Spleen	89.3	72.6	27.4
Brain	82.2	76.8	23.2
Kidney	73.4	64.5	35.5
Adrenal	61.4	54.3	45.7
Pancreas	57.4	38.9	61.1
Heart	52.9	45.0	55.0
G. I. tract	42.2	33.3	66.7
Lung	33.6	25.0	75.0
Liver	28.4	33.6	66.4
Diaphragm	5.6	0.0	100.0

Among the 500 autopsies studied there were 303 males and 197 females. The youngest case was a 6 months' fetus, born prematurely, and the oldest was a man aged 92 years. In order to condense the data, the cases were divided into three age groups, 0 to 29 years, 30 to 59 years and 60 to 92 years, which correspond approximately

to youth, middle and old age. Table 4 records the incidence of arteriosclerosis in both sexes for each of the age groups. It is difficult to correlate the occurrence of sclerosis in males and females because of an insufficient number of cases in the same groups, but on the whole it was approximately equal in the two sexes. The table indicates that the incidence and degree of arteriosclerosis increased with the age factor. It need occupy us only long enough to draw attention to three organs: the spleen, kidney and diaphragm. In the spleen and kidney the high incidence of arteriosclerosis became gradually more evident as the age factor advanced, until finally, in the group comprising those cases between 60 and 92 years, more than two-thirds of the cases showed marked sclerosis. In the diaphragm, however, the great majority of the arteries were free from sclerosis even in the advanced age group.

TABLE 4.—PERCENTAGE INCIDENCE OF ORGAN ARTERIOLARSCLEROSIS IN BOTH SEXES IN YOUTH, MIDDLE AND OLD AGE.

Degree of sclerosis.	Sex.	Heart.	Lung.	Spleen.	Kidney.	Liver.	Pancreas.	Brain.	G. I. tract.	Adrenal.	Diaphragm.
0 to 29 years (77 cases).											
Normal vessels	M	86.3	93.6	34.4	82.8	91.4	81.8	100.0	85.8	50.0	97.4
	F	89.0	89.4	27.8	85.0	94.0	86.6	75.0	83.4	87.5	100.0
Mild sclerosis	M	10.3	6.4	51.7	17.2	8.8	18.2	0.0	14.3	50.0	2.6
	F	11.1	8.6	55.6	10.0	6.1	13.4	25.0	0.0	0.0	0.0
Marked sclerosis	M	3.4	0.0	13.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	F	0.0	2.9	16.7	5.0	0.0	0.0	0.0	16.8	12.5	0.0
30 to 59 years (235 cases).											
Normal vessels	M	54.4	71.5	9.0	31.4	71.9	43.6	29.1	55.0	50.0	96.9
	F	32.8	67.3	8.0	47.1	65.4	33.3	18.7	64.3	38.5	96.4
Mild sclerosis	M	31.4	22.4	28.6	38.9	19.2	36.4	25.8	30.0	26.9	3.1
	F	47.2	26.9	27.3	25.9	19.4	25.0	37.4	14.3	30.8	3.6
Marked sclerosis	M	18.2	6.0	62.5	29.5	8.9	20.0	45.2	15.0	23.1	0.0
	F	20.0	6.0	65.0	26.9	15.3	41.7	43.8	21.4	30.8	0.0
60 to 92 years (182 cases).											
Normal vessels	M	16.0	41.6	5.4	8.5	62.6	20.0	0.0	42.8	5.6	91.6
	F	13.2	60.3	1.5	1.4	66.6	22.7	7.7	38.4	44.5	85.0
Mild sclerosis	M	25.2	41.6	9.8	16.0	24.0	34.3	9.1	21.4	38.9	8.3
	F	25.0	22.2	6.0	21.9	24.3	45.4	7.7	30.8	22.2	15.1
Marked sclerosis	M	58.8	16.9	84.9	75.5	13.6	45.7	91.0	35.7	55.6	0.0
	F	61.8	17.5	92.4	76.6	9.1	31.8	84.5	30.8	33.3	0.0

Discussion. With the exception of the results presented in Table 1 the study deals almost entirely with the arterioles and minute arteries of the organs.

Perhaps the most striking feature of the investigation was the rarity of sclerosis of the diaphragmatic arteries. This organ, one of continuous activity, has a very rich blood supply, yet seldom were its arteries found to be sclerosed and then but mildly. The relative infrequency of sclerosis in the arteries of the muscles is substantiated by the results of all workers with the exception of Kernohan and his collaborators, to which it is in marked contrast.

The spleen is of equal interest. All investigators seem agreed that it is more frequently the seat of arteriosclerosis than any other organ, with the possible exception of the kidney. More remarkable still, the spleen is usually affected to an advanced degree. Why this organ should be so peculiarly singled out for a degeneration of its arterial walls remains a mystery.

The investigations reported here and in the literature indicate that a truly generalized arteriosclerotic process of a degree sufficiently advanced to be of clinical importance occurs infrequently. It is true that marked sclerosis of the arteries of the spleen, kidney and brain is often found at autopsy and is in all probability a common occurrence during life; however, it is equally evident that other organs such as the lungs, liver, gastro-intestinal tract and particularly the voluntary muscles are seldom severely implicated.

The practical significance of the results is clear: a diagnosis of generalized arteriosclerosis should be made with caution and only on the basis of adequate evidence. The clinical features in such cases should be carefully correlated with the histologic findings at autopsy, for it is only in such a manner that clarity on this subject will be reached.

Summary. 1. An analysis of the incidence and severity of arteriosclerosis in the organs from 500 unselected autopsies is presented.

2. The order of frequency with which the arterioles and small arteries of the organs were affected was: spleen, brain, kidney, adrenal, pancreas, heart, gastro-intestinal tract, lungs, liver and diaphragm. This is in agreement with the observations of most investigators.

3. The arteries of the organs which were most frequently involved were also most markedly affected; conversely those that were least often involved showed mild degrees of arteriosclerosis.

4. The vessels of the diaphragm were infrequently implicated.

5. The incidence and degree of arteriosclerosis increased with the age factor.

6. The reports from the literature and the results of this study indicate that a generalized arteriosclerotic process of a degree sufficiently advanced to be of clinical importance occurs infrequently.

The author wishes to thank Dr. Balduin Lucké for suggesting this study and for much kind advice and criticism during its progress. He is also indebted to Dr. R. P. Custer for placing at his disposal the postmortem records and the microscopic sections of the cases from the Philadelphia General Hospital.

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ALLERGY IN HYPERTENSION.

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In 1930 Waldbott[1] reported some cases of essential hypertension who were members of allergic families, in whom there were sensitivities to foods or other allergens. The blood pressure in these individuals was lowered when the allergens to which they were sensitive were avoided, and returned to a high level on contact with them. He concluded that " some cases of unexplained hypertension may be caused by allergy."

This is a very attractive hypothesis because, if proved to be true, it will offer an effective method of treating hypertension.

Since one of us (M.H.F.) had available a large number of patients with hypertension who had been studied for a long period of time, and in whom the variations in pressure from month to month on various types of treatment were known, we decided to investigate this subject. It seemed to us desirable to begin with patients with hypertension who also had allergic manifestations, and to use cases without these symptoms only if favorable results were obtained.

Among several hundred patients with hypertension in the clinic

of Mt. Sinai Hospital only a few were found who had allergic symptoms. Since hypertension has an incidence increasing with age and allergy one decreasing with age, this dearth of material presenting both conditions is not surprising.

The following 2 cases from the clinic and 1 from private practice were selected:

Case Reports. CASE 1.—C. M., a white woman, aged 50 years, first came to our attention, June 8, 1929, complaining of substernal pressure, breathlessness on slight exertion, palpitation and cough. The symptoms were of about 3 years' duration, but had been growing progressively worse. The past history was essentially negative. Physical examination showed an obese female moderately dyspneic and orthopneic. The lungs were emphysematous. The apex beat of the heart was palpable in the 5th interspace at the anterior axillary line. There was a systolic murmur audible at the apex and the base. The second aortic sound was accentuated. The heart rate was 120 per minute, rhythmic and regular. The blood pressure was 226 systolic and 110 diastolic. The arteries showed moderate peripheral sclerosis. The edge of the liver was difficult to palpate, but there was tenderness below the right costal margin. There were varicose veins in both legs and slight pretibial edema. The blood Wassermann test was negative. The Roentgen ray showed moderate diffuse dilatation of the aorta, left ventricular hypertrophy and pulmonary congestion. The eye grounds showed tortuous vessels and the picture of retinal arteriosclerosis. The electrocardiogram was negative except for an inverted *T* wave in Lead III. The urine showed a small amount of albumin and a moderate number of leukocytes. The blood count and the blood chemical studies showed normal findings. In August, 1930, the patient was referred to the allergy department because of recurrent attacks of hives. She was found to be sensitive to cottonseed and was desensitized during September and October, 1931, and cottonseed products were removed from her diet. She has had no further allergic skin manifestations. Although she stated that she feels better since being treated in the allergy department there has been no lowering of the blood pressure level. Her blood pressure, taken on August 16, 1932, was 220 systolic and 130 diastolic.

CASE 2.—A. R., a colored female, aged 54 years, was first seen on March 30, 1928, complaining of pain in the eyeballs, occipital headaches, dizzy spells, palpitation on slight exertion, occasional slight swelling of the ankles and a general feeling of weakness. She had been told that she had had high blood pressure 6 years before, and had had a slight stroke 3 years before, which left her with a barely perceptible weakness of the left arm and leg. The past history was otherwise negative. Physical examination showed a well-developed and well-nourished colored female, not dyspneic nor orthopneic. The lungs were negative. The apex beat of the heart was just beyond the left midclavicular line in the 5th interspace. There was a faint systolic murmur at the apex and the second aortic sound was accentuated. The heart rate was 58 per minute, rhythmic and regular. The blood pressure was 220 systolic and 120 diastolic, and there was slight peripheral sclerosis. The liver was not enlarged and there was no edema. The orthodiagram showed considerable enlargement of the heart to the left with moderate dilatation and increased density of the aorta. The electrocardiogram was normal except for left axis deviation. The blood Wassermann test was negative. The urine showed a specific gravity varying between 1012 and 1023, albumin varying from 0 to +, and microscopically a few leukocytes. The patient was followed in our hypertension clinic from April, 1928, to September, 1929, when she was referred to the allergy department.

During this period she had had several transitory attacks of urticaria associated with some edema of the angioneurotic type. In the allergy department she was found to be sensitive to meats (beef, pork and mutton) and molluscs (clam, oyster, crab, lobster, scallop, shrimp) and told to abstain from the above-mentioned products. She has had no further attacks of urticaria or angioneurotic edema, but her blood pressure has not fallen to any degree (Chart I).

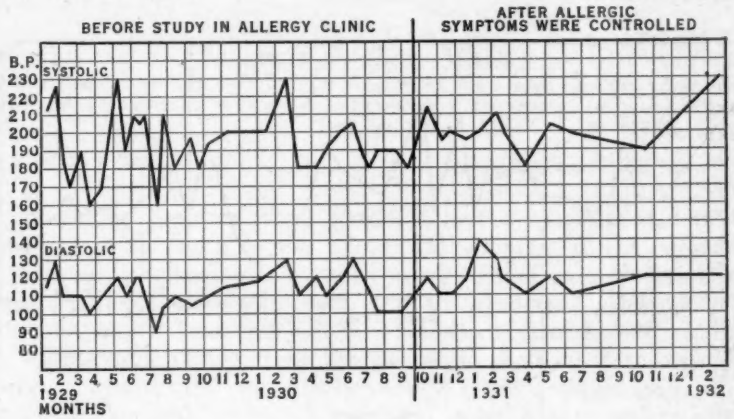

CHART I.

CASE 3.—G. A., a white woman, aged 30 years, was referred to us on July 8, 1930, because of attacks of asthma of 3 years' duration. She was known to have had hypertension for several years. No organic changes had been demonstrated; the urine and blood findings were normal. During a 14-month period of observation the blood pressure varied from 150 to 180 systolic and from 95 to 110 diastolic. Study from the allergic standpoint revealed the causes for the asthma to be dog dander, house dust and orris root, and when these substances were avoided and appropriate hyposensitization was carried out the attacks ceased and did not recur during a period of observation of 11 months. There was no change in the hypertension.

Discussion. Before one can draw conclusions as to the effect of any type of therapy on hypertension it is necessary to be familiar with the variations in the blood pressure level from time to time which occur spontaneously without treatment, and to compare the changes following treatment with those previously noted.

A study of Chart I shows that patient No. 2 had variations in blood pressure from 230 to 160 systolic, and from 130 to 90 diastolic before treatment, and that these swings in the blood pressure level were of frequent occurrence. Any changes produced by treatments would have to be persistent and would have to alter this blood pressure curve to a significant degree. This is not the case, since the variations in blood pressure after control of the allergic manifestations were not appreciably different from those in the control study periods. That this blood pressure record is an average one

is shown by Chart II, taken from a previous study[2] in which it was demonstrated that the sodium chlorid content of the diet did not affect the blood pressure level. Symptomatic improvement in hypertension follows many types of treatment, but the blood pressure changes are within control limits despite the symptomatic improvement.

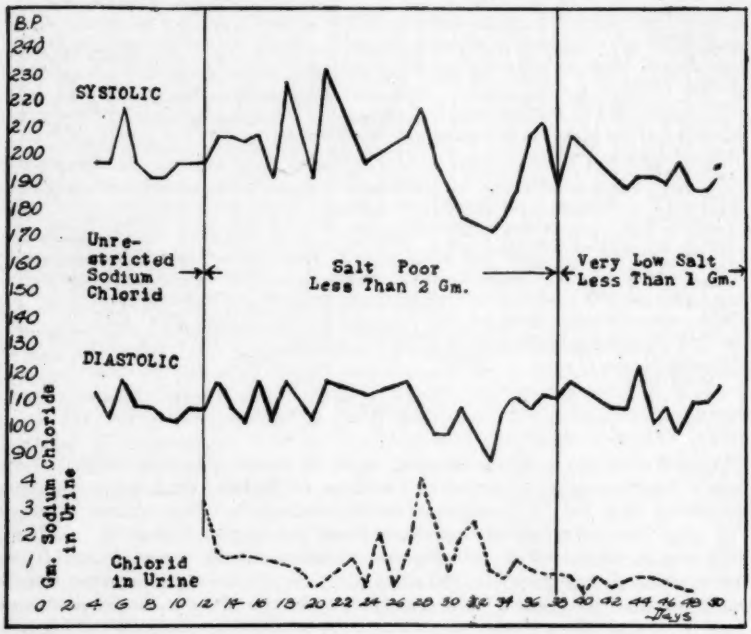

CHART II.

Summary and Conclusions. Three cases of hypertension without kidney failure, having allergic symptoms in addition to their hypertension, were studied by allergic methods.

The allergic symptoms were controlled in all of them. All patients felt better but the hypertension persisted. No relationship between the blood pressure level and the allergens could be demonstrated. Furthermore, hypertension and allergy are found infrequently associated in the same patient.

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UNUSUAL CHANGES IN THE ELECTROCARDIOGRAMS OF PATIENTS WITH RECENT CORONARY OCCLUSION.*

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Herrick,[1] Smith,[2,3,4] and Pardee[5,6] first demonstrated definite changes in the form of the electrocardiogram in recent coronary occlusions. Following their work many further case reports have appeared, so that certain features of the electrocardiographic picture have now been fairly well established. The earliest change is a noticeable deviation of the *S-T* segment from the isoelectric level. Later the *S-T* segment becomes isoelectric, shows an upward convexity and is followed by a negative pointed *T* wave with rounded shoulders. In successive records the *T* wave waxes and wanes in amplitude until only an inverted *T* wave remains. This large, negative *T* wave is the coronary *T* wave of Pardee[6] and the "coveplane *T*" of Rothschild, Mann and Oppenheimer.[7] Parkinson and Bedford[8] have divided the electrocardiographic changes into two types, *viz.*, the T_1 type with the *S-T* segment elevated and the *T* wave negative in Lead I, and the T_3 type in which these changes in the *S-T* segment and *T* wave occur in Lead III. However, the literature also contains many cases of recent coronary occlusions diagnosed clinically or proven postmortem, in which the electrocardiographic findings do not fit into the characteristic pattern.

It is now also well recognized that the rapidity and extent of the change in the electrocardiogram in successive records is more striking in recent coronary occlusion than in probably any other type of lesion. It is therefore the common practice to take a series of curves in cases of suspected recent coronary occlusion. In reviewing many of the published series, transitions are seen which, if judged by a single curve, without the series, would not be considered typical. Some of these earlier changes are so significant that we believe they may often furnish a clue to the presence of a coronary occlusion before more typical electrocardiographic changes occur. In fact, they may be present in cases of coronary occlusion which never develop the characteristic electrocardiographic form. In this study we attempted to identify some of the changes in a series of electro-

* Aided by the Emil and Fanny Wedeles Fund for the Study of Diseases of the Heart and Circulation.

cardiograms which we believe to be significant of coronary involvement but which are not accepted generally as diagnostic, and to illustrate and compare some of the less commonly seen changes in the more typical forms.

All of the patients here reported—except Case 11—had attacks clinically diagnosed as recent coronary occlusions and their histories are typical of the commonly accepted criteria for this diagnosis (see case reports). Case 11 is a "rheumatic heart" case presented to contrast the electrocardiographic appearance with that of Cases 9 and 10.

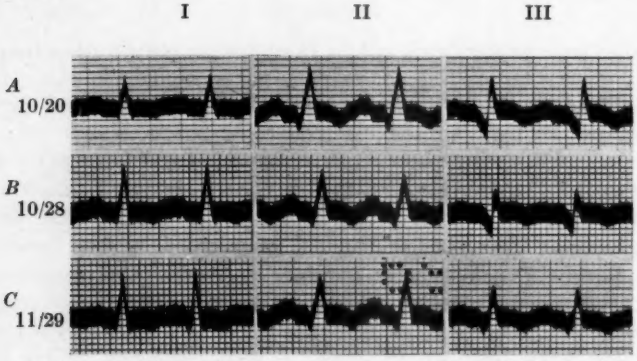

FIG. 1.—(Case 1.) *A*, 1 day after an attack; *B*, 8 days later after another severe attack on the same day. Patient died on December 31, 1931, and autopsy showed a thrombosis of the descending branch of the left coronary artery.

Atypical S-T Segment and T Wave Changes. Case 1 (Fig. 1) shows negative *T* wave in all 3 leads. Similar cases have been reported by Parkinson and Bedford,[8] Smith,[4] Willius and Barnes,[9] and Willius.[10] There is "low voltage" in this case, and a definite *Q* wave is present in Leads II and III to which Pardee,[11] Parkinson and Bedford[8] and Wilson *et al.*[12] ascribe some significance. The electrocardiographic findings in this case are suspicious although not typical of recent coronary occlusion. This patient died on December 1, 1931, and at autopsy a recent thrombosis of the descending branch of the left coronary artery was found.

Transient elevation of the *T* wave is shown in Cases 2 (Fig. 2), 3 (Fig. 3), and 4 (Fig. 4). Such slight, rapid changes are, we believe, to be regarded as suspicious of a recent coronary occlusion. In none of these cases did the electrocardiograms obtained ever assume the form regarded as characteristic, although the clinical picture in each case was that of coronary occlusion (see case reports).

Case 2 (Fig. 2) died on February 23, 1932, and at autopsy advanced coronary sclerosis and myocardial fibrosis were present. In view of the autopsy his attack may be regarded as an angina pectoris, and this patient resembles the case reported by Katz and

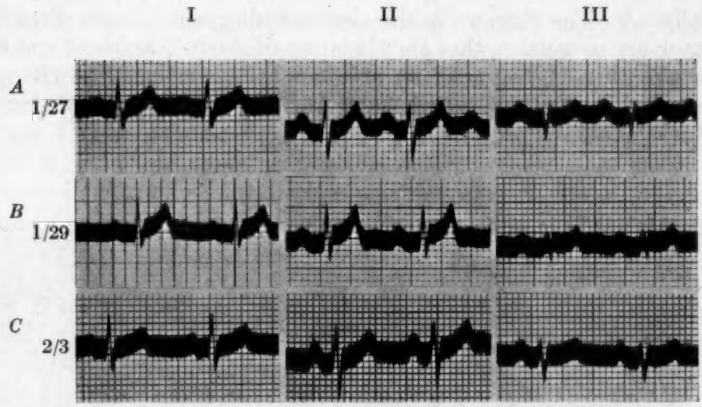

FIG. 2.—(Case 2.) *A*, 2 days before attack of pain; *B*, 6 hours after the attack. Patient died on February 23, 1932. Autopsy showed coronary sclerosis and myocardial fibrosis, but no occlusion of coronary arteries.

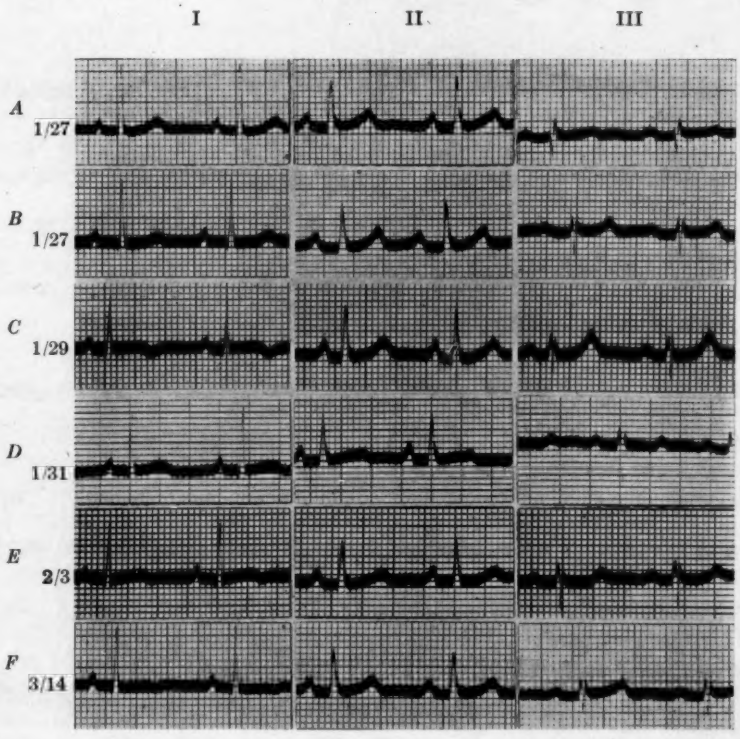

FIG. 3.—(Case 3.) *A*, a few hours after the attack; *B*, 7 hours later on the same day.

Wallace.[13] The changes in the electrocardiogram 6 hours after the attack are unusual in that the elevation of the *S-T* segment and the *T* wave (Fig. 2, Segment *B*) are just the reverse of the changes described by Feil and Siegel,[14] and Parkinson and Bedford[15] during attacks of angina pectoris.

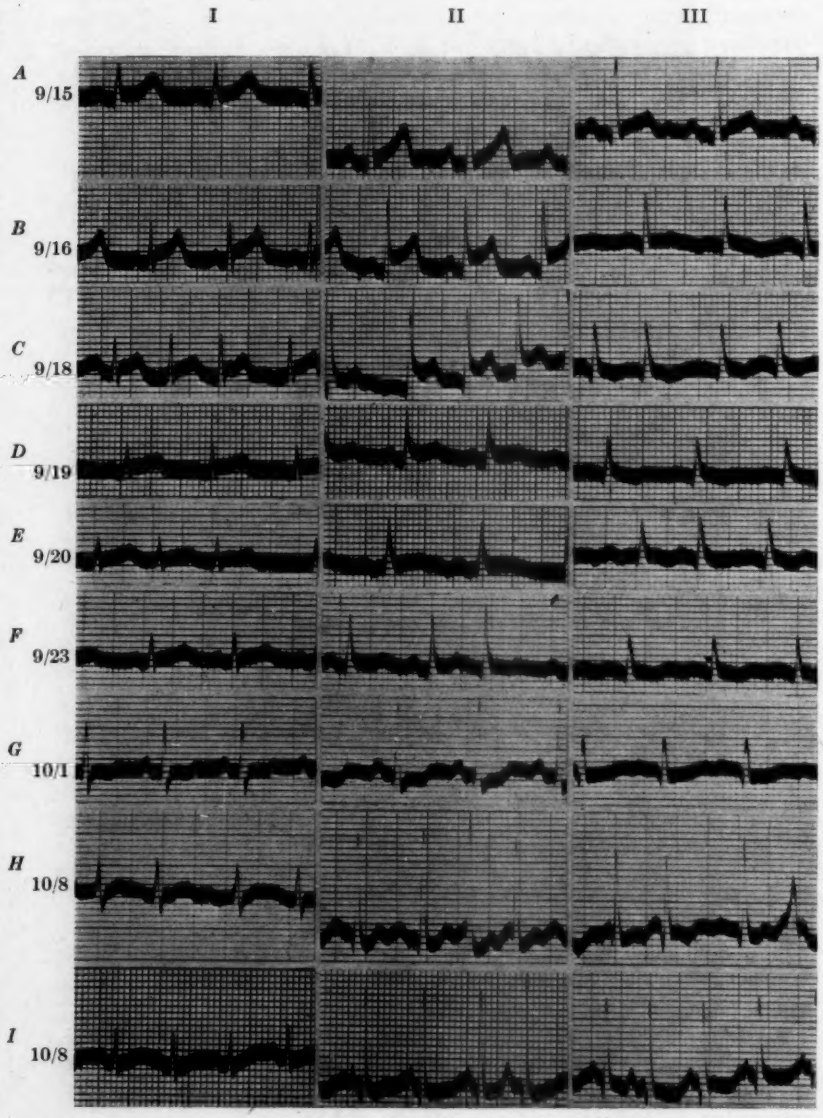

FIG. 4.—(Case 4.) *A*, a few hours after the attack; *G*, pneumonia developed.

Case 3 progressed until a definite inversion of the *T* wave appeared in Lead I and the elevation of the *T* wave increased in Lead III (Fig. 3, Segment *C*). In the course of the next few days further slight changes in the form of the *T* waves occurred.

Case 4 (Fig. 4) shows transient *T* wave changes which in Segments *B* and *C* are accompanied by a definite elevation of the *S-T* segments. Auricular fibrillation was present at times (Fig. 4, Segments *C*, *E*, and *H*). Following the development of pneumonia on October 1, 1932, a negative *S-T* segment appeared in all leads (Segment *G*) which decreased before death. The cause of this reversal may be due to a generalized ischemia of the heart following pneumonia. Such a generalized ischemia has been shown experimentally by Feil, Katz, Moore and Scott[16] to lead to such depressed *S-T* levels in the dog.

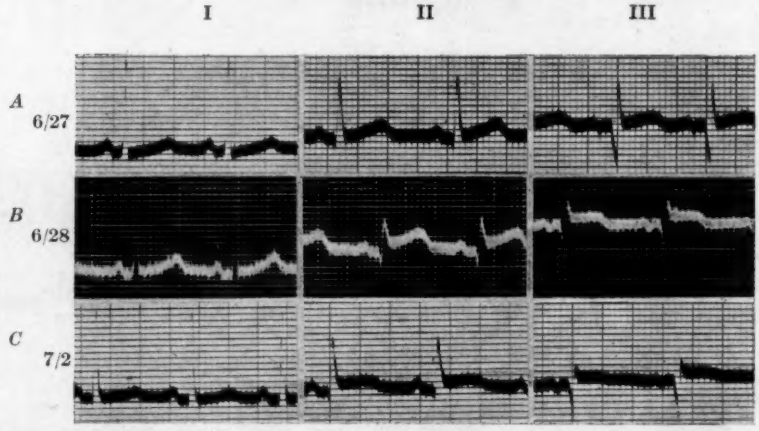

FIG. 5.—(Case 5.) *A*, 5 days after attack.

The most striking feature of Case 5 was the *S-T* elevation (Fig. 5). The first two curves were taken a few days after the attack and show a definite elevation of the *S-T* segment in Leads II and III. Four days later (Fig. 5, Segment *C*) the *S-T* levels in Leads II and III became somewhat lower and the *T* wave smaller in all leads. Unfortunately, no further records were taken, so it is impossible to know whether or not the characteristic coronary type of curve developed subsequently. However, the *S-T* elevation and the slight *T* wave changes, together with the *Q* wave in Leads II and III seem sufficient electrocardiographic evidence of a coronary occlusion in such a case.

A depression of the *S-T* segment in all 3 leads is the striking feature in Case 6 (Fig. 6). The *T* wave is upright in Lead I and it is difficult to identify the *T* wave in Leads II and III. There is a

peculiar notching of the *S-T* segment and the difference in the duration of the *S-T* segment in the separate leads is unusual. The notch on the *S-T* segment was located in the same spot of the cycle in the auricular extrasystoles (last beat L. II, Segment *B*, Fig. 6) as in the sinus beats, ruling out the possibility that these notches were *F*

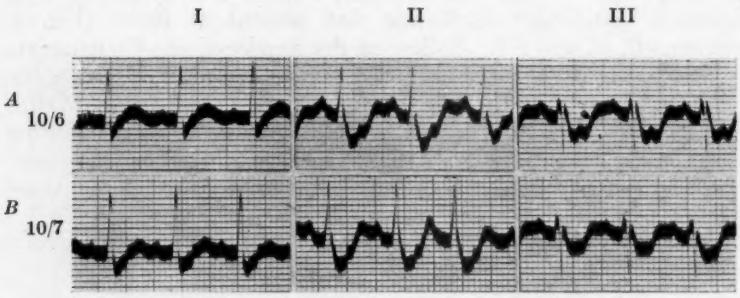

FIG. 6.—(Case 6.) *A*, 4 days after attack.

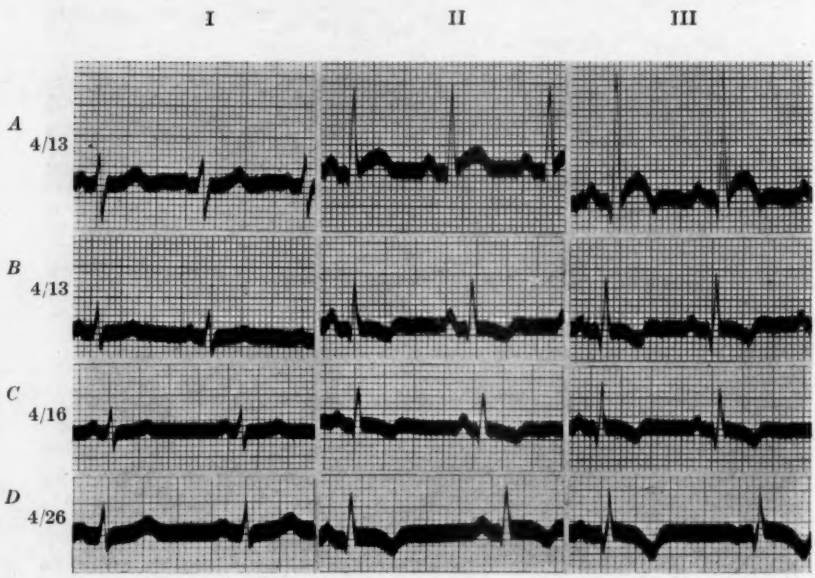

FIG. 7.—(Case 7.) *A*, the day of attack; *B*, several hours later on the same day.

waves and the mechanism auricular flutter. This case is presented to show that sharply depressed *S-T* segments may be present without the so-called high "take-off" and, while rare, are probably just as diagnostic of recent coronary occlusion as a high elevation of this interval.

The records of Cases 1, 2, 5 and 6 and some of the records of Cases 3 and 4 do not fit into the T_1 or T_3 types of Parkinson and Bedford classification.

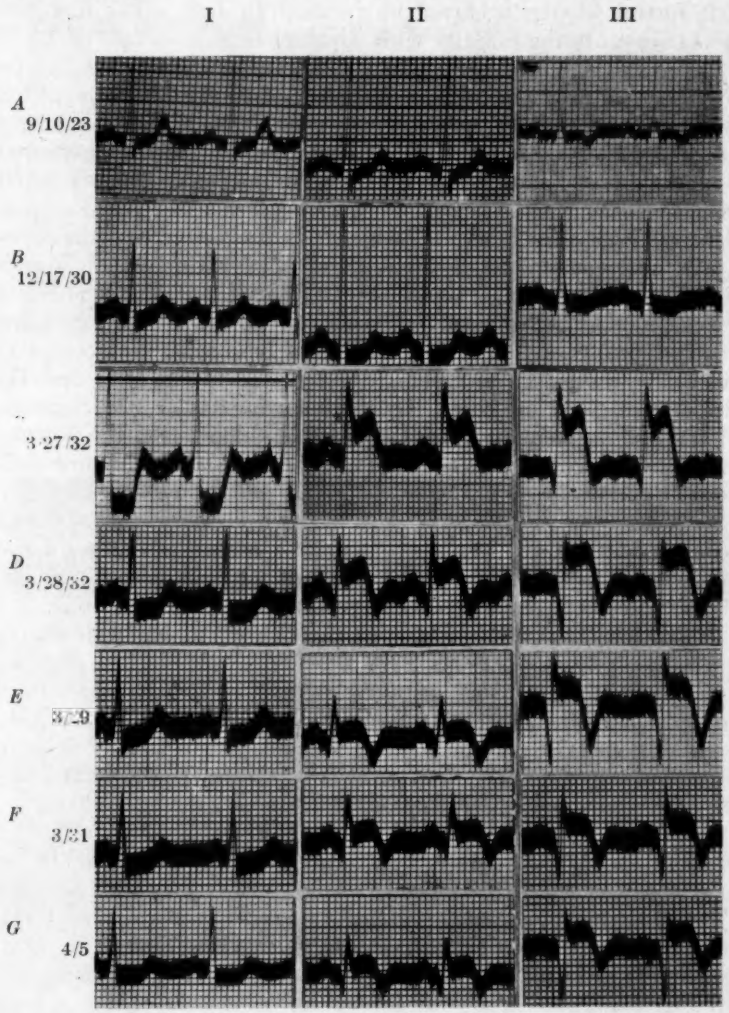

FIG. 8.—(Case 8.) *A*, 9 years before a severe attack; *B*, 2 years before attack. Patient has precordial pain; *C*, a few hours after attack.

Rare Forms of the T_3 Type. The T_3 type is well illustrated in Cases 7 and 8 (Figs. 7 and 8). The first record of Fig. 7 (Segment *A*) was taken very soon after the attack which occurred in the hospital. There is a definite elevation of the *S-T* segment in Leads II and III with the typical "hump," and a *Q* wave is also present in Lead III.

Another curve taken a few hours later (Fig. 7, Segment *B*) shows the typical cove-shaped inversion of the *T* wave in Leads II and III, and the *S-T* segment has returned to the isoelectric level. Very little further change occurred in the next 13 days. The first two curves illustrate the rapidity with which changes may take place.

In Case 8 there is an even more striking illustration of the T_3 type with a perfect example of the monophasic stage (Fig. 8, Segment *C*). The first tracing (Fig. 8, Segment *A*) was taken in 1923, shortly after the first symptoms of discomfort were observed, and showed nothing definitely abnormal. The second (Fig. 8, Segment *B*) taken in 1930 showed a negative *S-T* segment in all leads and a small negative *T* wave in Lead III, which was suggestive of some myocardial involvement. A few hours after a severe attack on March 27, 1932, another tracing was taken (Fig. 8, Segment *C*). This is a typical monophasic curve, with the entire ventricular complex greatly depressed in Lead I except for an early spike (*Q–R–S* complex) and a late wave (*T*), and markedly elevated in Leads II and III with only an early spike (*Q*). On the following day (Fig. 8, Segment *D*) the *S-T* segment in Lead I became less depressed, the *T* wave remaining upright. The *T* waves in Leads II and III became definitely negative and cove-shaped although the "hump" of the *S-T* segment remained. The *S-T* segments and *T* waves in subsequent records gradually changed in a typical manner, but the curves in the 2 months following were still decidedly abnormal and the *S-T* segments in Leads II and III had not reached the isoelectric level.

Probably the majority of cases go through the monophasic transitory stage within a few hours or possibly even minutes after an attack, and since in many instances records are not obtained until a day or so after the attack the monophasic stage is comparatively rarely obtained. It is unusual for the transition to be as slow as in Case 8. Pardee,[6] Scott,[17] Katz and Wallace,[13] and Moore and Campbell[18] have reported similar monophasic curves.

Unusual T_1 Type, with the Upright T Wave Unusually Tall in Leads II and III. Cases 9 (Fig. 9) and 10 (Fig. 10) resemble the T_1 type described by Parkinson and Bedford[8] in that the *T* wave is inverted and cove-shaped in Lead I and upright in Lead III. However, the outstanding feature of these curves is the tall, upright, peaked *T* waves in Leads II and III (Fig. 9, Segments *A*, *B* and *C*, and Fig. 10, Segments *D* and *E*). These *T* waves in Leads II and III, if seen in a mirror in an inverted view—in other words, in inverse image—exactly resemble the inverted cove-shaped *T* wave characteristic of coronary occlusion. Fig. 11 shows the 3 leads of Case 9 printed in inverse fashion and except for the inverted "*P*" and "*Q–R–S*" waves, this record looks like a classical T_3 type of curve taken some time after a coronary attack (*viz.*, the curves of Fig. 8).

Case 10 (Fig. 10) shows the transition of the *T* wave in Lead I from

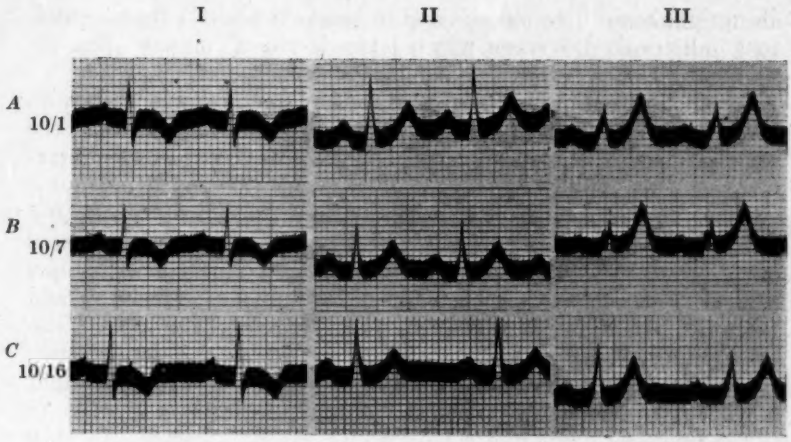

FIG. 9.—(Case 9.) *A*, 1 month following attack.

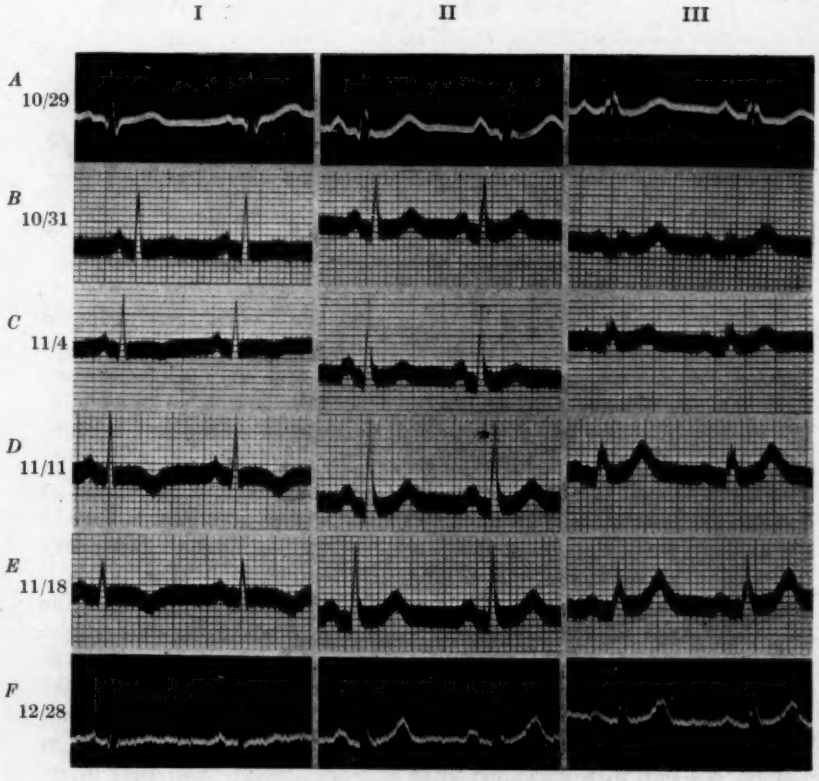

FIG. 10.—(Case 10.) *A*, the day of attack.

an upright to an inverted one and in Leads II and III from a small to a tall, peaked *T* wave which later decreased in size (Fig. 10, Segment *F*).

So much attention has been paid to the large negative *T* wave in coronary occlusion that sight has been lost of the fact that the inverse image of this in an upright large *T* wave is just as characteristic. In published series illustrating electrocardiographic changes in coronary cases this change in an upright *T* wave to a taller and more peaked one is often present, although seldom pointed out as being especially significant in itself. Levine's series[19] shows several such curves, *viz.*, Fig. 16, 19, 39 and 49; Parkinson and Bedford[8] (*viz.*, Cases 7, 8 and 10) and Moore and Campbell[18] also have published such records, and Wilson *et al.*[12] have described such curves. But none of these authors has pointed out that the upright *T* wave is so similar in shape and contour to the inverse image of the characteristic inverted cove-shaped coronary *T* wave. In view of these reported cases changes in an upright *T* wave, such as we have shown in Cases 9 and 10, are just as significant of a recent

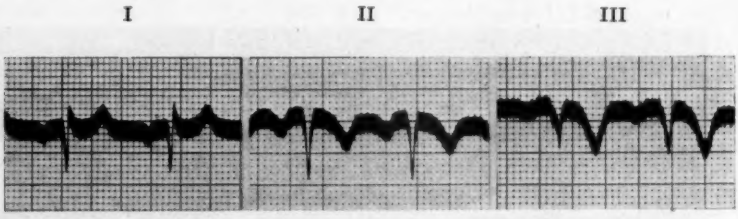

FIG. 11.—Segment *A* of Fig. 9, printed in inverse form.

coronary occlusion as their inverse image, the inverted, cove-shaped *T* wave. Furthermore, the inverted, cove-shaped *T* wave may be absent or, if present, may be much smaller and less noticeable than the upright *T* wave here shown.

Elevation of the *T* wave is known to occur in a number of conditions such as rheumatic heart disease, thyroid disease, pneumonia, and others, but the contour of the *T* wave and the *S-T* segment in such cases is different from the elevation here described. Fig. 12 is an example of the elevated *T* wave not specific for recent coronary occlusion. The second curve (Fig. 12, Segment *B*) taken in 1931, about 1 year after the first tracing and at the time a murmur was first detected, shows an elevation of the *T* wave in all 3 leads. The *T* wave in Lead II is especially tall. The contour of the *T* wave is quite different from that seen in recent coronary occlusion in that it has no rounded shoulders, its two limbs are not symmetrical, the descent being much steeper than the ascent, and the transition of its descent with the horizontal is more abrupt than that of its rise. The *S-T* segment also lacks the "hump." The contrast

between the upright *T* waves in non-specific and in coronary occlusion can best be seen by comparing this curve with Figs. 9 and 10.

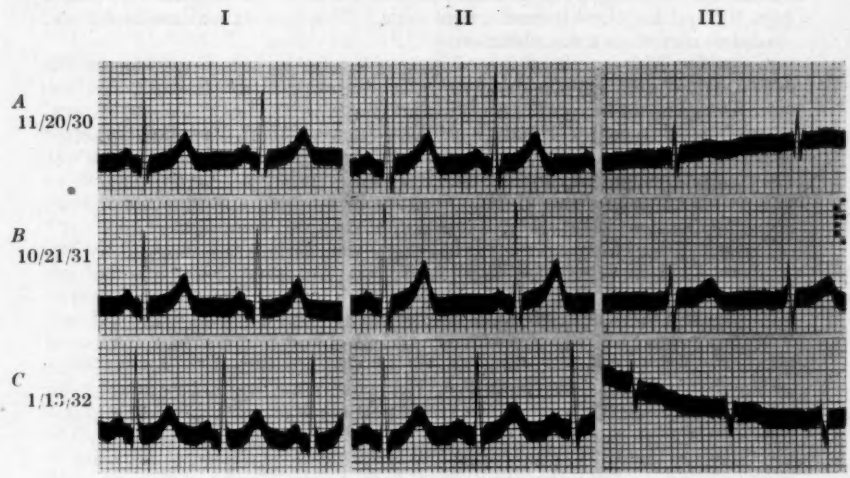

FIG. 12.—(Case 11.) A case of rheumatic heart disease.

Case Reports. CASE 1.—S. N., male, aged 59 years, 2 years before entrance into the hospital had his first coronary attack; 18 months later he had another, after which he was in bed much of the time. The day before entering (November 19, 1931, on Dr. Sidney Strauss' service) he had a typical severe attack which left him prostrated. While in the hospital he grew steadily worse, having frequent attacks of pain and dyspnea. He died on December 31. At autopsy a thrombosis of the descending branch of the left coronary artery was found.

CASE 2.—S. G., male, aged 67 years, was sent into the hospital in January, 1932, by Dr. B. Rappaport, with definite signs of hyperthyroidism; the basal metabolic rate was +42.7. While preparations were made for operation he had a sudden attack which was diagnosed clinically as a coronary occlusion. He had typical pain, a fall in blood pressure, elevation of temperature, rapid pulse, etc. Later he developed a bronchopneumonia, and died 3 weeks later (February 23). At autopsy advanced coronary sclerosis and myocardial fibrosis were present. Many atheromatous plaques were found in the coronary arteries which narrowed the lumen but did not completely occlude any vessel.

CASE 3.—M. E., male, aged 63 years, had no symptoms until 10 days before his attack, when he became short of breath on slight exertion. He was sent into the hospital by Dr. J. Meyer on January 27, 1930, with a characteristic attack of coronary occlusion with pain, leukocytosis of 18,400, and a drop in blood pressure. When he left the hospital he was entirely free of pain and discomfort.

CASE 4.—A. S., male, aged 47 years, entered the hospital on Dr. Schiller's service, September, 1930, because of an infected hand, and had no history of previous angina pectoris. While in the hospital he was suddenly seized with a very severe substernal pain which radiated toward the neck. Respiration became rapid and labored. His face was ashen; the lips had a cyanotic

tinge. His temperature was 101° F. and the blood pressure dropped to 70 mm. Hg systolic and 50 mm. Hg diastolic. The leukocyte count was 12,600. A diagnosis of a recent coronary occlusion was made. The patient continued to be very ill and auricular fibrillation developed. Roentgen rays showed a diffuse bronchopneumonia. The patient became worse and died, but no autopsy was obtained.

CASE 5.—M., female, aged, 63 years, 2 months before coming to the hospital had attacks of substernal pain radiating to both arms. At the time she was sent in by Dr. W. Buchbinder (June 27, 1930) she had clinical symptoms of recent coronary occlusion such as pain, dyspnea, cyanosis and a leukocytosis of 15,000. Somewhat later a precordial friction rub was heard and she had a temperature of 103° F. She had severe attacks of paroxysmal dyspnea and the blood pressure dropped considerably. After a month in the hospital she was much improved and went home.

CASE 6.—N. H., female, aged 63 years, was sent to the hospital by Dr. F. Beaumont on October 6, 1930, in a stuporous condition. She had felt quite well until a few days before when she had a severe attack of pain in the epigastrium. This came on very suddenly and she was "doubled up" with the severity of it. She had not urinated and had not had any bowel movements for 2 days before coming to the hospital. There was some pitting edema of the extremities. Her pulse rate was 120 and of poor quality. The blood pressure was 70 to 80 mm. Hg systolic. The leukocyte count was elevated. The urine contained albumin and casts. The next day her condition was worse. She became more cyanotic, respirations were labored and the lungs filled up with fluid. That evening she died quite suddenly. The heart rate a few minutes before death was 120. No autopsy was obtained.

CASE 7.—B. R., male, aged 72 years, entered the hospital April 13, 1932 on Dr. I. Koll's service, with a hematuria. This was found at cystoscopic examination to be due to a papilloma of the bladder. Some hours after this examination the patient suddenly became very ill with symptoms typical of a coronary accident. He had pain, vomiting, increased temperature, a fall in blood pressure, and a leukocytosis of 16,600. The pain was present for several days, but he gradually improved and in several weeks was discharged from the hospital.

CASE 8.—F. N., male, aged 62 years, for about 10 years had complained of a feeling of pressure in the precordial area which usually came on after meals. One week before entrance into the hospital he began to have extreme pain which radiated to the left arm. On the day of a severe attack (April 27, 1932), he was sent into the hospital by Dr. Sidney Strauss with clinical symptoms typical of a coronary accident. He gradually improved but had occasional attacks of tachycardia. When discharged a month after admission he was free from pain.

CASE 9.—L. F., male, aged 60 years, about 1 month before entering the hospital was suddenly seized with a severe pain in the epigastrium which almost immediately radiated into the precordial area. This was accompanied by a sense of constriction across the anterior thorax and a choking feeling in the throat. Following rest in bed and medication the patient felt entirely well in a few days and went back to work. Two weeks later he had another attack, and from that time until entrance into the hospital he had repeated attacks of pain usually relieved by nitrites. He was sent into the hospital by Dr. W. Hamburger on October 1, 1931. He improved steadily during his stay in the hospital and was discharged improved after a few weeks.

CASE 10.—A. G., male, aged 75 years, 3 days after the extraction of a tooth had a severe attack of epigastric pain radiating to the left arm and shoulder. The pain was very severe. He became acutely ill, had nausea

and vomiting and received no relief from any medication. Twenty-four hours later he was sent into the hospital by Dr. Sidney Portis (October 30, 1931). At this time his blood pressure was 110 mm. Hg systolic, and 70 mm. Hg diastolic; his temperature was 102° F., and his leukocyte count was 14,450. He was kept in bed, and after a month was discharged.

CASE 11.—M. F., male, aged 12 years, was under observation in the Children's Cardiac Clinic, for 3 years before entrance to the hospital. He had definite rheumatic pain and heart disease was suspected, although it was a year after the pain started before a definite cardiac murmur to the left of the sternum was heard. The child gradually became worse following the appearance of this murmur, and the murmur grew rapidly louder and more definite. He was sent into the Sarah Morris hospital on January 11, 1932, on Dr. J. Gerstley's service, acutely ill. Positive blood cultures for Streptococcus viridans were obtained, and in a few days he died following emboli in the left popliteal and left axillary arteries. At autopsy there was found an acute ulcerative and vegetative endocarditis of the aorta and mitral valves superimposed upon a chronic rheumatic endocarditis. There was an insufficiency of the aortic valves and an acute myocarditis.

Summary and Conclusions. Electrocardiograms are presented of 10 cases having a clinical history typical of protracted or transient coronary occlusion of recent origin.

The most significant findings in cases of recent coronary occlusion are changes in the form of the *S-T* segment and the *T* wave: either an elevation, a depression, or an inversion. The most significant fact is that a definite change is present, whether it be in an upward or in a downward direction. Successive records usually show a rapid change in contour in the early stages of coronary occlusion. Not all curves in recent coronary cases can be fitted into the T_1 and T_3 types of Parkinson and Bedford.

Attention is drawn to a large, upright, sharply peaked *T* wave whose limbs and shoulders are symmetrical and have their convexity pointing downward and toward each other, associated with an isoelectric or negative *S-T* interval having a "hump" pointing down. It is different from the non-specific, tall *T* wave. This large, upright *T* wave is most commonly found in Leads II and III of the T_1 type and is as diagnostic a feature of the coronary occlusion type of curve as the inverted cove-shaped *T* wave of which it is the inverse image. We have designated this characteristic as the upright coronary *T* wave.

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SPECIFIC SERUM TREATMENT OF TYPE I LOBAR PNEUMONIA.

Regulation of Dosage by the Observation of Circulating Agglutinins With the Stained Slide Agglutinin Test. (Sabin.)

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Recovery from lobar pneumonia due to pneumococci has been shown to be associated with the appearance of humoral antibodies against the specific type of pneumococcus responsible for the infection. Neufeld[1] suggested that the demonstration of humoral antibodies might be used as an indication of the proper dosage of antipneumococcic immune serum in the treatment of pneumonia. Cole,[2] Sutliff,[3] and Sabin[4,5] have reported the demonstration of type specific agglutinins during the course of treatment with immune serum. We have attempted to determine the minimum dosage of antipneumococcic immune serum necessary to produce demonstrable agglutinins in the patient's blood and to correlate this with the therapeutic result. The technique used is that described by Sabin[4] and is simple enough to be carried out with a minimum of apparatus and labor. Its use resulted in the administration of less serum, thus sparing the patient some discomfort and expense. It is recommended to physicians who desire to control antipneumococcic serum administration carefully.

Materials and Methods. Twenty-four patients were studied less than 96 hours after the onset of Type I pneumococcic lobar pneumonia. Twelve

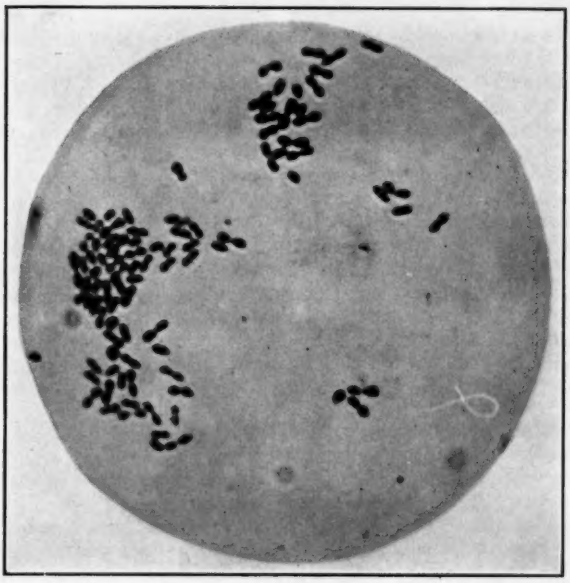

FIG. 1.—Positive agglutination of Type I pneumococci in patient's blood. (Oil immersion × 1800.)

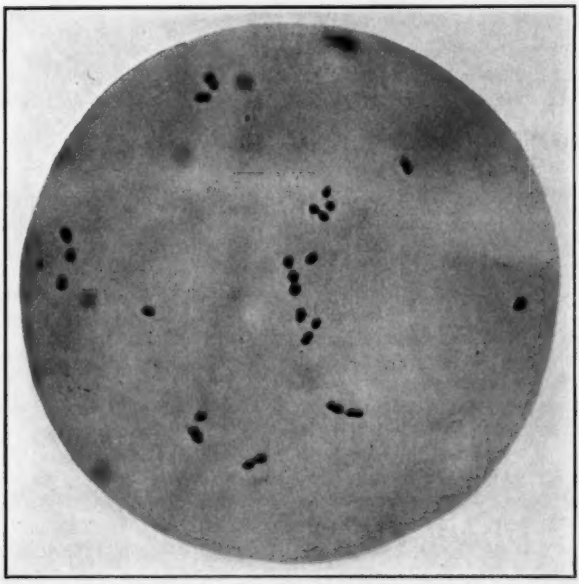

FIG. 2.—No agglutination of Type I pneumococci in patient's blood. (Oil immersion × 1800.)

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were treated as follows: The serum used was polyvalent concentrated antibody prepared by Felton's method, specific for Types I and II, and was supplied by the State Antitoxin and Vaccine Laboratory. Treatment was begun as soon as practicable after the determination of the type of the infecting organism. Blood was obtained for culture and agglutinin study before beginning treatment, at frequent intervals during therapy, and for some days following recovery. The serum was given in doses of 5, 10, or 15 cc. containing 2500 mouse protective units per cc. Twenty-five cc. were given during the first 4 hours (except in Case 12) but subsequent doses were given only when homologous type agglutinins were not demonstrable in the blood of the patient by the slide method. Agglutinin tests were made at 2-hour intervals on the first day of treatment and at 4-hour intervals thereafter as long as the patient showed signs of toxicity. Following symptomatic recovery, studies were made at daily or longer intervals to demonstrate the duration of the persistence of agglutinins. Twelve other patients were treated with a standard, empirically derived dosage of 75 cc. or more of the same serum.

The technique of determining the circulating antibodies in these observations was similar to that described by Sabin.[5] Two drops of blood, about the size of a drop from a 3 mm. platinum wire loop, obtained by puncture of the finger tip or ear lobe, were placed on a glass slide. By means of the platinum loop an equal amount of Type I pneumococcus antigen was quickly mixed with 1 drop of blood, and a similar sized drop of Type II pneumococcus antigen was mixed with the other. These mixtures, kept separate, were spread thin and allowed to dry. This can readily be done at the bedside using an alcohol lamp to flame the wire. The smears were then stained with 0.1 per cent aqueous safranin to which a few drops of 10 per cent acetic acid were added to hemolyze red blood corpuscles and examined under the oil-immersion lens. Agglutination, when present, was quite characteristic and easily recognized, the organisms being gathered in clusters of a definite pattern. Negative tests showed the organisms spread out uniformly over the slide (Figs. 1 and 2).

The antigens were prepared from an 8-hour growth of a culture of maximum mouse-virulence by washing twice in physiologic saline, and resuspending the organisms in saline to which 0.5 per cent of formalin was added.

Two cases (Cases 9 and 11) are described here to illustrate the course of treatment and the response to small doses of serum as administered on the basis of type-specific agglutinin determination. The charts show the relation of body temperature, blood culture, and circulating antibody to treatment.

Type Cases. CASE 9 (Fig. 3).—J. P., aged 35, white male, entered the hospital on April 6, 1932, 37 hours after a chill which marked the onset of his illness. He was in moderate distress, somewhat dyspneic, and cyanotic. Physical and Roentgen ray signs revealed consolidation of the right lower lobe. Sputum examination revealed pneumococcus Type I. Blood culture was negative on the day of admission, but showed pneumococcus Type I, just prior to treatment. Serum treatment was begun the following morning, 50 hours after the onset, the dosage being regulated by the presence or absence of agglutinins in the patient's blood as detected by the slide method. Agglutinins were found to be present after the second dose, a third dose being given at this time, making 25 cc. in all. Agglutinins were found to be present when sought at 2-hour intervals following treatment for 12 hours. There was a prompt drop in temperature with marked subjective improvement the following morning. Blood culture was negative at that time. The agglutination test after 24 hours left one in doubt as

to whether or not agglutinins were present, so a further dose of 10 cc. of serum was administered. Agglutinins for pneumococcus Type I were found to be present thereafter for 5 days while the presence of agglutinins for pneumococcus Type II was doubtful 48 hours after the last dose of serum and they were definitely absent after that. The temperature remained normal and the patient experienced a rapid and uneventful convalescence. No agglutinins were demonstrable in his blood either by the microscopic slide method or the macroscopic tube method 12 days after the last dose of serum.

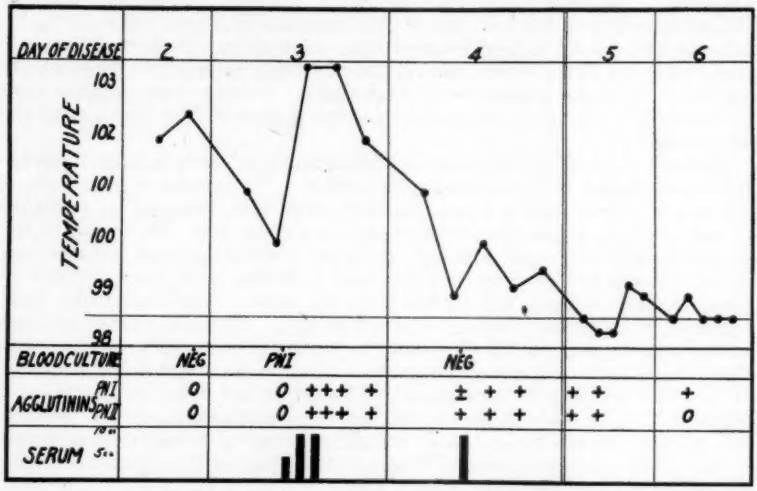

FIG. 3.—Case 9. Treatment begun on second day of disease; prompt recovery after 35 cc. of serum. PNI = Pneumococcus Type I.

This case is quite typical of many serum-treated patients because immediately after the administration of serum there was a rapid drop in temperature, clearing of the blood-stream infection and marked general improvement, subjectively and objectively. Five of the 12 cases showed this type of response after receiving total doses of from 15 cc. to 45 cc. of the concentrated antibody intravenously.

CASE 11 (Fig. 4).—R. R., aged 39, white, male musician, was admitted to the hospital on April 21, 1932. He had been well until 39 hours before admission when he was suddenly seized with a stabbing pain in the right lower chest which radiated to the upper abdomen. He felt very ill and feverish. About 4 hours before admission there was a sudden severe exacerbation of the pain in the upper abdomen; the pain continuing for 1 hour and gradually diminishing to the time of admission.

Physical examination revealed a well-developed, slightly undernourished white man, obviously very ill. The skin was hot and dry, the face and extremities slightly cyanotic. Respirations were rapid, short and jerky, accompanied by pain. There was an occasional hacking cough with a moderate amount of tenacious, yellowish sputum. The thorax revealed dullness to percussion with relative diminution in the intensity of the breath

sounds over the right lower back and axilla. The abdomen was slightly distended with marked spasticity below and rigidity and exquisite tenderness over the upper portion.

In view of the rigidity and tenderness of the upper abdomen an exploratory laparotomy was performed on the day of admission. Two loops of the jejunum were found to be of dark gray color with considerable distention of the bloodvessels, and the tail of the pancreas was somewhat indurated. There were several small gray opaque areas at the base of the mesentery which were thought to be fat necrosis. The surgical diagnosis was acute pancreatitis. A cholecystostomy was established and drains were placed in the region of the pancreas. The patient withstood the operation very well.

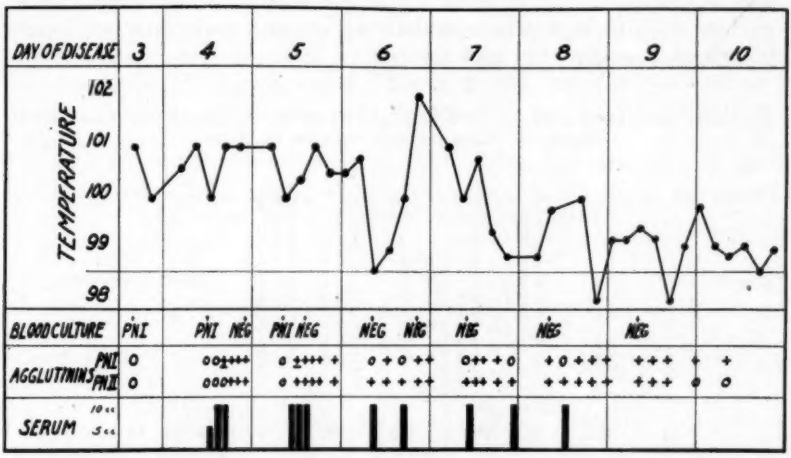

FIG. 4.—Case 11. Treatment begun on third day of disease; delayed response, subsequent abscess on buttock and empyema. Note repeated disappearance of agglutinins and their return after succeeding doses of serum. PNI = Pneumococcus Type I.

The following day he was found to have consolidation of the lower lobe of the right lung. Pneumococcus Type I was recovered from the sputum and blood culture (8 colonies per cc.) taken before the operation. Serum treatment was instituted as soon as the type was determined, 63 hours after the onset of the illness. As will be seen from the chart, circulating agglutinins appeared and the blood culture was sterile after 25 cc. of serum had been administered. The agglutinins disappeared and the blood culture again became positive (6 colonies per cc.) 16 hours after the last dose of serum. Further treatment with 30 cc. of serum brought about the reappearance of agglutinins with sterilization of the blood stream. The agglutinins disappeared from time to time during the next 3 days, returning after the administration of 10 cc. doses of the antibody solution, finally persisting after the patient had received a total of 105 cc.

The patient's condition remained grave. He was prostrated and greatly distressed by persistent hiccough until the 9th day of his illness when he showed marked subjective improvement and signs of resolution were found over the affected lung. On the 13th day he was considered to be well, as regards the acute symptoms of pneumonia. Subsequently he developed an abscess on the buttock and empyema of the right pleural cavity from both

of which pneumococcus Type I was obtained on culture. He recovered completely after appropriate surgical treatment.

This case is presented to show the phenomenon of absorption of the homologous agglutinins contained in the therapeutic serum when administered in the doses used in Case 11. It is interesting to note that while the agglutinins for pneumococcus Type I appeared and disappeared 5 times during the period of treatment agglutinins for pneumococcus Type II persisted except at the time the pneumococci returned in the blood the day after treatment was begun. Serum was given to this patient only when the slide agglutination test indicated the absence of agglutinins in his blood. By comparison with Case 9 it is seen that the serum requirement of these 2 patients varied within wide limits.

TABLE 1.—PATIENTS WITH TYPE I LOBAR PNEUMONIA TREATED WITH SPECIFIC SERUM ON BASIS OF AGGLUTININS IN BLOOD.

Case No.	Age, years.	Duration of disease to admission, hrs.	Duration of disease to onset of treatment, hrs.	Blood culture before treatment.	Total dosage serum, cc.	Duration from treatment to first sustained drop in temperature, hrs.	Duration from treatment to complete symptomatic improvement, hrs.	Result of treatment.
1	74	28	41	Pn. I	55	19	..	Died on 11th day; no pneumococci in cultures at autopsy.
2	63	In hosp.	24	Neg.	45	15	43	Prompt recovery.
3	27	In hosp.	26	Neg.	55	13	..	Empyema; recovered after thoracotomy.
4	46	55	84	Neg.	55	6	134	Prompt recovery; sterile subcutaneous abscess.
5	26	60	79	Neg.	25	19	72	Prompt recovery.
6	22	62	71	Neg.	35	164	212	Delayed recovery.
7	45	32	51	Neg.	25	19	47	Prompt recovery.
8	37	63	74	Neg.	40	55	107	Delayed recovery; delirium tremens.
9	35	37	50	Pn. I	35	23	31	Prompt recovery.
10	30	23	45	Pn. I	55	17	..	Delayed response; Strep. empyema; died; no pneumococci in cultures at autopsy.
11	42	39	63	Pn. I	105	45	141	Delayed response; empyema, recovered after thoracotomy.
12	36	51	80	Neg.	15	15	112	Prompt recovery.
Average	40	57	57	..	45	34	100	

Two tables are presented here to compare the results obtained by use of small doses of serum controlled by the agglutinin method

with the results obtained by using large doses of serum. Analysis of Table 1 reveals that 7 of the patients treated on the basis of the presence or absence of agglutinins recovered without complications, 5 promptly and 2 after a slightly delayed course. Two patients (Cases 1 and 10) died, 1 from a secondary streptococcus infection after apparent recovery from pneumonia (reported by Parsons and Myers[18]). Beta hemolytic streptococci were found in the lungs of each of these patients at autopsy, but no pneumococci were demonstrable. No further deaths occurred in the series, making the rate 16 per cent for this group of 12. Due to the small number of cases this has slight if any significance. Two patients (Cases 3 and 11) developed empyema due to pneumococcus Type I and recovered after thoracotomy and tidal irrigation. One patient (Case 4) developed a sterile abscess on the right arm at the site of a hypodermic injection which apparently was responsible for fever during his convalescence.

TABLE 2.—PATIENTS WITH TYPE I LOBAR PNEUMONIA TREATED WITH EMPIRICAL DOSE OF 75 CC. OR MORE OF SPECIFIC SERUM.

Case No.	Age, years.	Duration of disease to admission, hrs.	Duration of disease to onset of treatment, hrs.	Blood culture before treatment.	Total dosage serum, cc.	Duration from treatment to first sustained drop in temperature, hrs.	Duration from treatment to complete symptomatic improvement, hrs.	Result of treatment.
13	37	53	79	..	75	10	14	Prompt recovery.
14	52	68	86	..	75	18	118	Delayed recovery (serum sickness).
15	45	55	72	Neg.	75	8	120	Prompt recovery (serum sickness).
16	42	57	80	Neg.	75	63	71	Delayed recovery.
17	37	49	66	Neg.	75	8	72	Prompt recovery.
18	24	69	77	Neg.	75	12	64	Prompt recovery.
19	15	72	83	..	75	18	18	Prompt recovery.
20	52	24	48	..	75	0	45	Temperature dropped before treatment begun.
21	24	48	72	Pn. I	120	21	..	Empyema; recovered after thoracotomy.
22	38	77	95	..	75	6	6	Prompt recovery.
23	25	11	28	Pn. I	75	0	23	Temperature dropped before treatment begun.
24	35	48	70	..	75	47	47	Delayed recovery.
Average	36	52.5	71	..	79	18	54	

Table 2 shows that of the 12 patients treated with large empirical doses (75 cc. or more according to clinical condition of patient) 6 recovered promptly and 3 recovered without complications after

a delay of 2 or more days following serum administration. Two patients in this group had a drop in temperature before serum therapy was begun, suggesting spontaneous recovery. One had empyema due to pneumococcus Type I and recovered after thoracotomy and drainage. None of these patients died.

The duration of the disease to the first sustained drop in temperature was less than 23 hours in all but 3 patients (Table 1), with an average of 34 hours. In Table 2 the duration was less than 21 hours in all but 2 patients, with an average of 18 hours. On com-

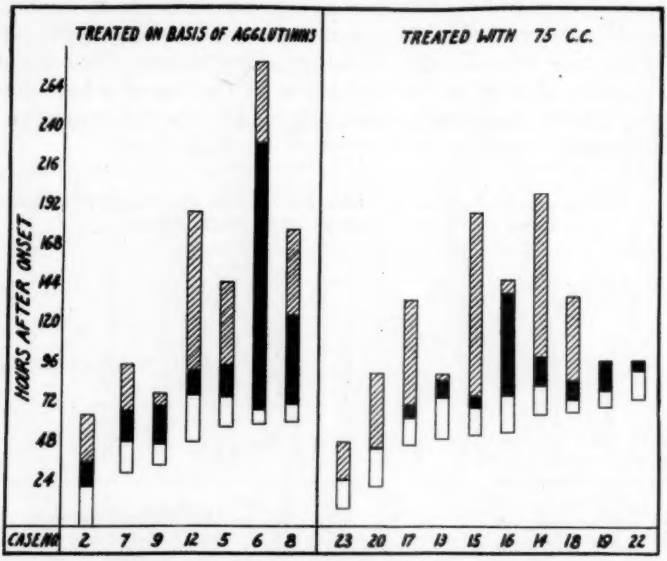

FIG. 5.—Duration of the disease in agglutinin controlled and empirically treated cases. Each bar represents 1 patient who had an uncomplicated course ending in recovery. The distance of the bar from the base line represents the duration of the disease before entry, the light portion the duration from entry to serum administration, the solid portion the duration to the first sustained decrease in temperature below 101° F., and the hatched portion the duration to the disappearance of all symptoms and fever.

paring this with the results in a similar series of specifically treated patients in which 17 of 18 showed a symptomatic response within 30 hours after treatment (Sutliff and Finland[17]), it is seen that the therapeutic effect in the present series was probably satisfactory in both groups of patients. The average duration of the disease is much shorter for the patients in Group II, who received larger doses of serum than in Group I, but, in view of the experience with this same method of treatment quoted above,[17] such an extraordinarily rapid average response cannot be expected to occur when more cases are included.

Figure 5 represents in graphic form the duration of the disease to admission, to onset of treatment, to initial sustained drop in temperature and to complete symptomatic recovery from the disease for the uncomplicated, recovered cases in the two groups of serum-treated patients.

Comparison of the total dosage used to treat the cases recorded in Table 1 with the amount used to treat the cases recorded in Table 2 shows that there was a considerable saving in the amount of serum used. The average amount for those patients in whom the dosage was regulated by the presence of agglutinins was 45 cc.; for those treated empirically the average amount was 79 cc. The amount of serum required to produce demonstrable circulating agglutinins in the 12 patients with lobar pneumonia due to pneumococcus Type I varied from 15 cc. to 105 cc. Most of these patients required from 25 cc. to 55 cc. to produce this effect.

Discussion. That specific antibodies play an important rôle in recovery from infectious diseases has been conjectured since the earliest days of the bacteriologic era. The reader is referred to the paper by Bailey[7] for a detailed analysis of the theory of agglutination and the part it plays in recovery from disease.

The appearance of circulating humoral antibodies in the blood of patients convalescent from lobar pneumonia was first demonstrated by Klemperer and Klemperer[8] who showed that the serum of such patients protected rabbits from otherwise fatal doses of pneumococci. Neufeld and Händel[9] pointed out that this protection was specific for the type of pneumococcus causing the pneumonia, that it appeared about the time of recovery and that specific agglutinins were present in the same blood samples. Dochez[10] found antibodies protective for mice against the homologous serum. Clough[11] found phagocytosis to be enhanced by homologous convalescent serum.

Cole[12] in presenting a series of studies on patients treated with antipneumococcic immune serum noted the occurrence of similar antibodies in the patients' blood after the injection of serum. Lord and Nesche[13] followed the mouse protective antibodies and agglutinins in a series of serum treated and a series of non-specifically treated patients. They found agglutinins to appear in 7 treated patients before demonstrable protective antibodies appeared and from this they concluded that the appearance of agglutinins would be a dangerous criterion on which to base the administration of serum. Finland and Sutliff,[14] on the other hand, have stated that protective antibodies are generally more readily detected than agglutinins and that in cases of Type I and II peunmococcic pneumonia agglutinins are not demonstrable in the absence of protective antibody. Sia, Robertson and Woo[15] found the power of whole fresh blood to kill virulent pneumococci, which is acquired during the course of lobar pneumonia, to be present in all cases where agglu-

tinins are demonstrable. Felton[16] in discussing the various antibodies in antipneumococcic immune serum states that ". . . attempts to separate the water insoluble proteins into fractions . . . have failed to disclose . . . fractions in which any . . . antibodies are separated. Thus one fraction containing the protective substance can be shown to contain the other immune reactions."

On the basis of the foregoing facts we are led to the assumption that where agglutinins are demonstrable protective antibody is present and that its persistence in the circulating blood indicates an excess, no matter how small, of the antibody needed to terminate the infection. The phenomenon of the absorption of antibody, first noted by Cole,[2] is evidence of the quantitative utilization of immune bodies by the infected individual. This phenomenon is admirably illustrated in Case 11, in which it is seen that the homologous agglutinins repeatedly disappeared some hours after the serum was administered as though neutralized. The Type II agglutinins, heterologous to the infecting organism, which were present in the therapeutic serum were found to persist. It is apparent that homologous agglutinins were present in the patient's blood only after he had received an excess of serum. A similar observation, less pronounced, is made in Case 9.

The slide agglutination method seems to be a practicable and effective method for determining the amount of serum to be administered, an amount which varies between wide limits. Hitherto it has been customary to determine the dosage of antipneumococcic serum by "the condition of the patient," a vague reliance on clinical judgment. Under such a therapeutic scheme there is grave danger that a patient may receive too little serum as the result of a temporary amelioration of symptoms. It is well known that following the administration of immune serum there may be misleading signs of recovery with subsequent relapse unless the therapy is continued. An empirical dose large enough to cover all cases effectively would entail for the majority of patients a great waste of an expensive pharmaceutical product. Serum sickness, which is more common among patients receiving large than small doses of antibody, may be avoided in a certain number of cases when doses no larger than necessary are given.

These observations, it is emphasized, were made on patients treated early in the course of the disease. It is not known whether these results would obtain in patients in whom the disease had existed for a longer period.

Summary and Conclusions. The effectiveness of two methods of dosage of specific serum in the therapy of pneumococcic Type I lobar pneumonia is compared in two groups of 12 cases each, treated before the 5th day of their disease. In the first group amounts of serum were given (15 to 105 cc., average 45 cc.), just sufficient to

maintain agglutinins in the circulating blood, as determined by a rapid bedside method. In the second group a larger, empirically selected dose (75 cc. or more, average 79 cc.) was given to each patient.

In both groups the response to the therapy was satisfactory as shown by the short duration of the disease after therapy, and by the death rate. On the average, the course of the disease in the 12 empirically treated patients was much shorter than the average course of a larger series of cases treated in the same manner, but this unusual result in a small series of cases does not necessarily indicate the superiority of this method of therapy.

Evidence is given to indicate that the persistence of agglutinins for the homologous organism is an index that a sufficient amount of antipneumococcic serum has been administered to produce a satisfactory therapeutic result.

The authors are indebted to Dr. Claude E. Welch for assistance.

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SEASONAL INFLUENZA.

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Until the agent immediately responsible for influenza is discovered, no specific diagnostic procedure for identification of the disease is likely to become available. Its recognition on purely clinical grounds, however, is easy enough in the midst of epidemics

such as occurred in 1830, 1836, 1847, 1889 and 1918. Whether or not the sporadic cases commonly encountered at other times and called by some name as La Grippe, grip, or pseudo-influenza are really due to the same etiologic factor cannot be determined with certainty at this time. In both, the Pfeiffer bacillus is frequently found, but today few believe it to be the exciting cause. To say that both are due to a filtrable virus means nothing so long as the specific virus is undetermined. The decision for the present must rest on clinical grounds.

From a description of the disease as it occurred in the epidemics we may conclude that influenza is an acute febrile illness of unknown etiology, sudden in onset, and generally attended by headache, backache and pains in the extremities; catarrhal symptoms are frequent; the duration usually short, although frequently followed by prostration, and there is a notable tendency to pneumonia. In addition to this more or less general description of the disease, there are other characteristics brought out in a study of the individual case. The period of incubation is usually between 24 and 48 hours; the onset is not only sudden, as a rule, but the patient is frequently able to recite the exact moment when he was taken ill (Stengel[1]). A slow or disproportionate pulse is frequent and cyanosis often a characteristic. A low diastolic pressure is reported by one observer (Riesman[1]). One feature of influenza which is usually present and upon which great stress is laid in diagnosis, is the leukopenia that occurs in the disease. Bronchopneumonia is the most frequent serious complication and is usually spoken of as influenzal pneumonia because of the atypical signs of the disease and protracted course with persistent cough often simulating tuberculosis (Landis[1]). Other frequent complications are sinusitis, otitis media and various psychoses. The tonsils are said to be an important focus of infection in influenza (Davis[1]). Immunity, if it exists at all, is probably of very short duration. Any natural immunity that may have been present is easily lost if the individual's resistance is lowered.[3] Acquired immunity is disproven by the patients who had several attacks of the disease in the 1918 epidemic.[4]

The epidemiologic characteristics of influenza are important, because on these the diagnosis is chiefly based.[5] First, the great explosiveness of the disease, rapid increase in the number of cases in a community reaching a peak in 2 to 3 weeks and gradually fading in about the same length of time. Next, the high dispersiveness or rapidity with which the disease spreads from place to place. Other characteristics are: the high morbidity with low case fatality; independence of weather and season; the increased death rate among young adults, a robustness of temperament being almost a predisposing factor; and lastly the recurrence of epidemics of the disease.

Between these pandemics of influenza there occur every year

during the winter months localized outbreaks of an acute febrile disease varying in intensity from year to year and having many of the characteristics of epidemic influenza. Many observers have noticed the similarity of this seasonal disease and epidemic influenza, but concluded that they were not the same.[1,2] Parsons,[6] in 1891, expressed the view of the dissimilarity of the two diseases and based his belief largely on the mortality in the several age groups: the high mortality of influenza in young adults was apparent in epidemics of the disease. The pandemic form of influenza is said to differ in the greater explosiveness and more rapid spread of the disease; catarrhal symptoms are less frequent; mental depression more marked; pneumonia more frequent and of a different type; greater and more prolonged prostration following the acute attack; leukopenia more common, and the incidence and mortality of the disease higher, especially in young adults.

Our knowledge of the life history of influenza between pandemics is very meager and so long as we are ignorant of the causative organism it will be difficult to recognize sporadic cases. It may be that there are different strains of the influenza organism and that this organism is with us always[10] and is capable of a change of virulence which may account for the pandemics of the disease from time to time.[5] The endemic cases of influenza which are caused by the less virulent organism occur during the winter months when our resistance is lowest and epidemiologic factors most favorable. When these seasonal outbreaks are investigated, many of the characteristics of so-called true influenza become more apparent. Miller[8] reported a group of cases which occurred at the University of Oregon in November and December of 1928. There were 319 cases, 250 of which were hospitalized. In this group there were 9 complications; 4 of which were pneumonia, 3 of these being the so-called typical influenzal bronchopneumonia; 3 cases of otitis media; 1 of follicular tonsillitis; and 1 antrum infection. There was 1 death. The disease as reported resembled very much the influenza as seen in pandemics, the chief difference being in the severity of the infection.

To illustrate what was perhaps a typical outbreak of seasonal influenza, a group of 140 unselected cases was collected from the records of the Student Health Service of the University of Pennsylvania for the school year 1931, 1932. A similar outbreak occurred in 1930, 1931, and a more severe one in 1929, 1930. All of the cases referred to in the report were in students between the ages of 17 and 27 years, and all were confined to the infirmary of the Student Health Service. The cases, 124 in males and 16 in females, occurred among the 5800 students eligible for treatment in the Health Service. The first case was admitted December 8, 1931, and the last one was discharged June 22, 1932. The onset was usually sudden, frequently characterized by coryza or other catarrhal

inflammation of the upper respiratory tract; within 12 to 24 hours pains in the extremities developed, and in many cases pains in the eyeballs; the temperature during the first day rose gradually to its peak, which averaged 100.9° F. in the 128 uncomplicated cases. In only 49 of these uncomplicated cases did the temperature ever exceed 101° F. and in 8 instances it reached 103° F. The duration of the fever in the uncomplicated cases averaged 2.9 days and usually terminated by lysis. During the illness the patient as a rule did not appear very sick, his complaints were few, and frequently his symptoms did not warrant his temperature. It was often difficult to convince the student that he should be confined to bed. In other words, the disease lacked the great prostration shown in the epidemics. Cyanosis[1] and the peculiar flushed appearance of the countenance sometimes associated with the disease did not occur. The patients were not mentally depressed. No noticeable effect on the cardiovascular system was observed. In the average case the pulse rate was proportionate with the fever. The average pulse pressure was 42.6, with a normal blood pressure for this age group being about 120 systolic and 80 diastolic. Of the 42 cases that showed positive urinary findings, only albuminuria, usually a trace, and occasionally a trace of sugar, were noted. This would be expected in any group of acute infectious fevers. No case of nephritis developed.

The most important confirmatory evidence of the diagnosis of influenza was in the white blood cell count. In 70 per cent of the uncomplicated cases the white cell count was less than 7000 and in 12 of the 15 cases in which the count was 10,000 or more some complication, as bronchopneumonia, could be demonstrated. The average white cell count in uncomplicated cases was 5400. The connection between the white blood count and the course of the disease was studied. No appreciable relationship existed between the white cell count and the degree of fever. The average maximum temperature for uncomplicated cases in which the count was 7000 or over, was 101.3° F., as compared with an average temperature of 100.9° F. for all uncomplicated cases. The duration of fever was little affected by differences in cell count. The average duration of fever for cases with cell count less than 7000 was 2.8 days, as compared with 3.2 days in cases with a cell count of 7000 or over. Another similarity between this group of cases and the influenza as seen in the epidemics was shown in the complications that developed. The most frequent serious complication of epidemic influenza is bronchopneumonia. In this group there were 12 with complications; 6 with bronchopneumonia; 3 with otitis media; 2 with follicular tonsillitis, and 1 with maxillary sinusitis. The bronchopneumonia presented indefinite signs and in 2 cases the persistent chest findings and cough made it difficult to rule out tuberculosis.

The contagiousness of the disease was considered. In one dormi-

tory in which there were 43 students only 6 developed the disease. Most of these students had separate rooms and, when the patient had been living with another student, his roommate showed no special tendency to develop the disease. In another dormitory accommodating 37 students 5 cases occurred. In still another, 5 out of 29. All of the 16 girls who contracted the disease lived in one dormitory, in which there were 150. The presence of tonsils was investigated as a possible predisposing cause. In 70 per cent of the cases in this group the tonsils had been removed. The question of immunity conferred by previous attacks of influenza was considered and an attempt made to determine this from the history. In the 63 cases in which a definite history could be obtained, 46 had never had influenza before, 18 had, 2 of these having had the disease twice before.

Conclusions. In the absence of some positive criterion for the diagnosis of influenza the characteristic acute febrile illnesses occurring every winter should be regarded as influenza.

The chief points of similarity are: the "explosiveness" and "dispersiveness" of the two diseases; the high incidence in young adults; the sudden onset and short duration; general symptoms; leukopenia; and the frequent complication of an atypical bronchopneumonia.

The seasonal influenza, as it may be termed, is probably due to a milder strain of the influenza organism, which accounts for the comparative mildness of the disease. The virulence of the organism causing seasonal influenza may increase, and under favorable circumstances give rise to pandemics of influenza.

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CHRONIC ADRENAL INSUFFICIENCY: AN HITHERTO UNDESCRIBED SYNDROME: WITH CASE REPORT.*

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Although great advances have been made in our knowledge of the pathology and pathologic physiology of the adrenal glands, their possible function and relation to the other organs of the body, are still largely matters of conjecture. Perhaps the recent isolation of active cortical extracts will solve the riddle and with it a host of correlated questions, such as their relationship to Addison's disease, to appetite, to malnutrition and to vitamin B. Clinical cases in which the lesion is apparently primary in the suprarenals, can often shed some light on these problems. We believe that the following case, with its unique clinical syndrome and its unusual etiology, serves such a rôle.

Case Report. E. S., male, Hungarian, aged 50 years, was admitted to the medical service of this hospital November 30, 1931. Because of language difficulties and the lack of coöperation on the part of the patient, the history was unsatisfactory. Upon inquiry, he admitted that he had not eaten any food for a week and that his diet had been inadequate for several months previously. Nothing could be elicited about his past history, except that he had been in Bellevue Hospital on several occasions for acute alcoholism.

Physical Examination. Temperature, 96° F.; pulse, 70; respirations, 20; blood pressure, 148 systolic and 80 diastolic.

He was greatly undernourished and looked acutely ill. His face had a grayish pallor and an anxious expression. A marked anasarca of the entire torso and all four extremities was present, most pronounced in both lateral thoracic regions. The face and neck were not involved. The mucous membranes were pale. A cataract was present in the right eye, the left was normal. There was impaired resonance over the left apex of the lung and absolute flatness below the third rib anteriorly and the spine of the scapula posteriorly. Over the apex, tubular breath sounds and a few moist râles were audible. Breath and voice sounds and fremitus were absent over the area of flatness. The right lung was hyperresonant. The apex beat of the heart was neither visible nor palpable. The borders could not be determined. The sounds were of poor quality but no murmurs were audible. The pulses were equal, regular and the radial walls were somewhat thickened. The abdomen was negative. The prostate felt moderately enlarged, smooth and firm. The reflexes were normal.

Laboratory Reports. Red blood cells, 4,150,000 per c.mm.; hemoglobin, 84 per cent (Sahli); white blood cells, 11,300 per c.mm.; neutrophils, 86; lymphocytes, 12; mononuclears, 2 per cent. Urine: Cloudy amber;

* Read at Section of Medicine of the New York Academy of Medicine, January 17, 1933.

specific gravity, 1.022; reaction, acid; sugar, negative; albumin, negative; an occasional hyalin and granular cast, a few leukocytes and no red blood cells. The blood Wassermann reaction was negative. The cerebrospinal fluid was normal. It contained no cells and no globulin. Wassermann and colloidal mastic tests were negative. Chemical examination of the blood plasma showed non-protein nitrogen, 37 mg. per cent; sugar, 123 mg. per cent.

An electrocardiogram showed slurring of the *Q–R–S* complexes and flattening of the *T* wave in Leads I and III.

Roentgen rays of the chest revealed obliteration of the left pulmonic field from apex to base and a large, dense, sharply circumscribed shadow near the hilus of the right lung.

Course. He was put on a high caloric, vitamin B-rich, salt-poor diet. Fluids were limited to 1000 cc. and he received one injection of salyrgan. Two days after admission, 2030 cc. of straw-colored fluid with the characteristics of a transudate were aspirated from the left chest. Tumor cells or tubercle bacilli could not be demonstrated. A roentgenogram taken after the aspiration showed a persistence of the mass in the right chest and bronchoscopy was then performed with entirely normal findings. Roentgen rays of the long bones, skull and gastro-intestinal tract were negative.

The patient ate voraciously and a remarkable improvement in his general condition was soon noticeable. He became mentally alert, jovial and active. The edema began to perceptibly diminish on the fourth day after admission and had entirely disappeared by December 14. The mass near the hilus of the right lung also vanished and Roentgen ray (December 17) revealed nothing but some interlobar pleural thickening in this region. Repeated urinalyses were normal. His blood pressure rose to 178 systolic and 100 diastolic. His blood count at this period was red blood cells, 3,750,000; hemoglobin, 68 per cent; white blood cells, 8100; neutrophils, 78; lymphocytes, 18; mononuclears, 3 per cent.

The improvement, however, lasted for but 10 days. Quite suddenly his voracious appetite was superseded by profound anorexia and rapid and astounding emaciation. The progressive deterioration was accompanied by marked asthenia, melancholia and desire for death. He became very tremulous and involuntary athetoid movements in the fingers were noted. The superficial and deep reflexes disappeared entirely with the exception of the left plantar reflex. Joint sensation was universally impaired and there was loss of perception of touch and pain in the extremities. For a short time, a slight left facial weakness was present. A few days after these observations, he began to complain of severe burning pains in all the extremities, and their muscles and nerves were extremely tender.

By the early part of January, in spite of forced feedings and glucose and calcium gluconate intravenously, the appearance of the patient was truly cadaveric. He was semi-stuporous, irrational when aroused and incontinent of both urine and feces. The athetoid movements persisted. *The panniculus adiposus had universally and completely disappeared.* The eyeballs and cheeks were sunken, the bony borders of the chest and abdomen and the muscles of the extremities (especially the abductors of the thighs and the flexors of the forearm) were prominent and the abdomen was markedly scaphoid. In spite of the extraordinary wasting, the skin retained its elasticity and accommodated itself to the loss of the subcutaneous fat. It was smooth, soft, and exhibited a prolonged Sergeant's line. *There was no pigmentation.* Although every conceivable precaution was taken, bedsores could not be prevented. No matter in what position the patient was placed, the skin over a bony prominence became gangrenous. His blood pressure was 154 systolic and 88 diastolic. Chemical examination of the blood plasma revealed the non-protein nitrogen to have risen to 61 mg. per

cent. The blood was dark red and viscid. The similarity between the patient's clinical picture and the state of chronic adrenal insufficiency in the experimental animal was noted.

On January 18, he had a chill and his temperature rose to 105° F. Signs of a bronchopneumonia appeared. He became comatose, his face assumed a grayish, pinched, mask-like expression and he slowly sank until his death on January 23. His temperature was subnormal terminally.

Autopsy. The body is markedly emaciated, weighing 70 pounds. There is a large decubitus ulcer over the sacrum measuring 6 cm. in diameter and smaller ones over the dorsal surfaces of the elbows and both ilia. *The subcutaneous fat is completely absent.*

Both pleural cavities are free of fluid. A few, easily separated, fibrous adhesions bind the left upper lobe to the thoracic wall. Interlobar adhesions are present between the right upper and middle lobes. The right lung weighs 315 gm. and the left 290 gm. The surfaces of both lungs are bluish in color, mottled with black. On section, they are red, smooth and moist. A few dark red, raised, granular, airless patches are present in both lower lobes.

The pericardial cavity is normal and contains about 10 cc. of clear, yellow fluid. The heart is markedly atrophic, weighing 160 gm., is brown in color and the epicardial fat is entirely absent. The coronary vessels are tortuous and surrounded by gelatinous tissue. The right ventricle and auricle are slightly dilated. The aortic, mitral, tricuspid and pulmonary leaflets are normal. The aorta exhibits a few atheromatous and calcified plaques in its ascending and thoracic portions. The coronary arteries are patent throughout.

There are moderately dense adhesions between the diaphragm and the anterior surfaces of both lobes of the liver and between the gall bladder and transverse colon. *There is complete absence of intra-abdominal fat—omental, mesenteric and perirenal.*

The *liver* is small, dark brown in color and cuts with slightly increased resistance. It weighs 850 gm. The central veins are engorged and the parenchyma has a yellowish-brown, homogeneous appearance.

The *spleen* is small, soft, covered by dense adhesions, and weighs 70 gm. The capsule is thickened. On section, the pulp is semi-diffluent and light red in color. The fibrous stroma is increased.

The *stomach* is small, contains some bile stained mucus and the mucosa exhibits irregular areas of congestion and hemorrhage.

The *intestines* show no gross abnormalities.

The *pancreas* is small and atrophic. The splenic artery is tortuous and sclerotic.

Both *kidneys* are small, each weighing 95 gm. The capsules strip with moderate ease leaving a very finely granular surface. On section, the cortex is slightly narrowed, and the markings are rather indistinct. The blood-vessels are prominent. There is no pelvic fat.

The *adrenals* appear enlarged in proportion to the marked atrophy of the other organs. The right adrenal weighs 9.2 gm. and the left 8.7 gm. No abnormalities are visible on the surface, and the suprarenal vessels are grossly normal. On section, the right adrenal exhibits a gray, grumous mass about 1 cm. in diameter which occupies the region of the medulla and the inner layer of the cortex. The normal lipoid of the remaining portion of the cortex is replaced by grayish, homogeneous tissue. The left adrenal is similar in appearance to the right, except that the cheesy area is much smaller than that in the right adrenal and portions of the medulla are discernible.

The *urinary bladder* is small and contracted. The *prostate* is small, soft and grossly negative. The *testicles* are atrophic.

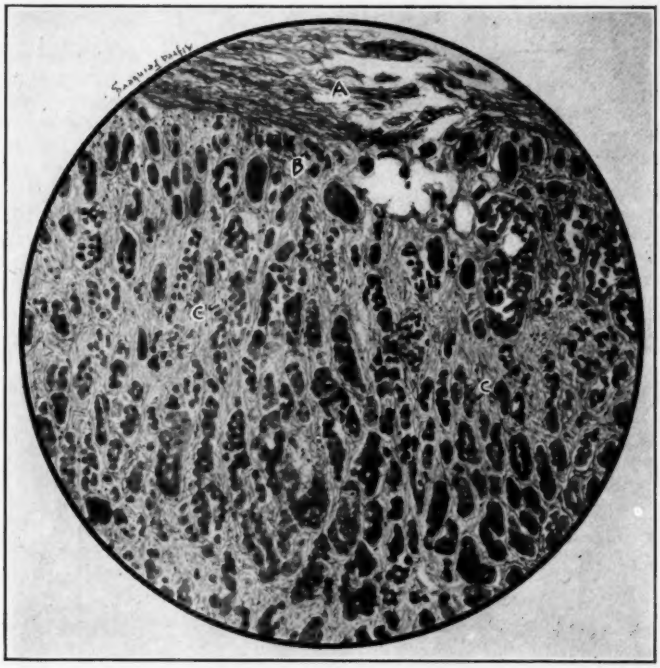

FIG. 1.—Section of right adrenal cortex, showing *A*, capsule; *B*, islands of regenerating cells in the zona glomerulosa, and *C*, collections of degenerating cells in the zona fasciculata separated by apparently thickened reticulum and giving this portion of the cortex a gland-like appearance. × 80.

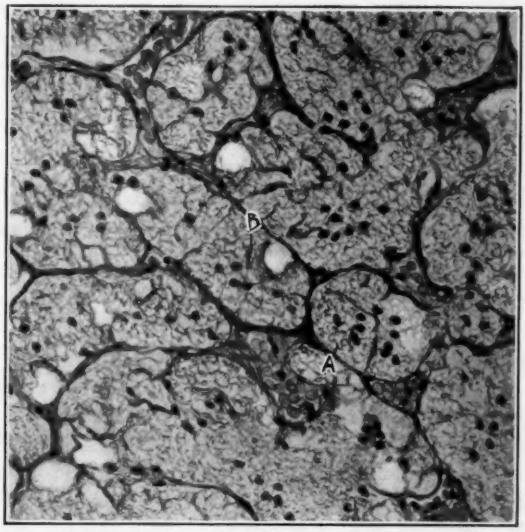

FIG. 2.—High magnification of zona fasciculata, showing *A*, enlarged weblike cells in which the nuclei are still well-preserved, and *B*, cells in which the degeneration is more advanced with fading out and disappearance of nuclei. × 400.

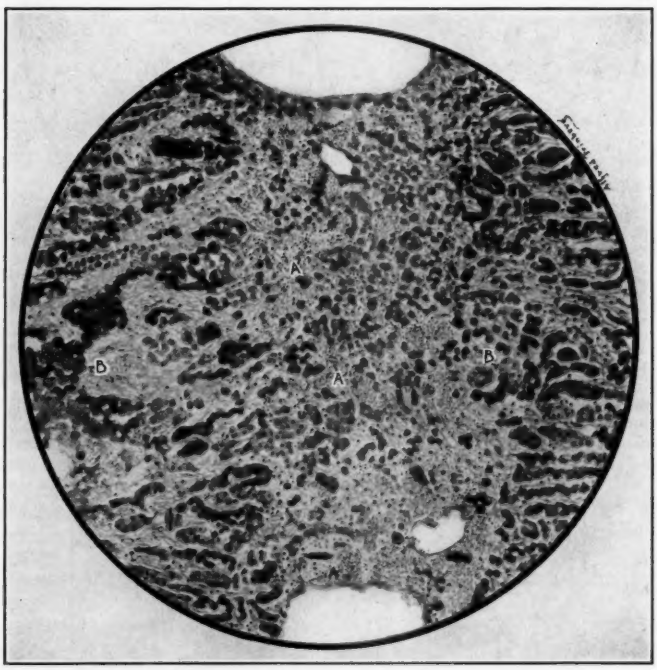

FIG. 3.—Section through central portion of right adrenal, showing *A*, deposits of extracellular hemosiderin pigment in zona reticulata and medulla; *B*, degenerating and necrotic cells of zona fasciculata, and *C*, absence of medullary tissue with only the reticulum still visible. × 80.

The *thyroid* is small and somewhat firmer than normal. No *thymic* vestiges are found.

There is some increase in the subarachnoid and intraventricular fluid. The *meninges* are congested. The vessels of the circle of Willis show no sclerosis. The *brain* and *spinal cord* are grossly negative. *The pituitary gland shows no gross abnormalities.*

Microscopic examination confirms the marked atrophy of all the internal organs and the presence of a bronchopneumonia and an arteriosclerotic nephritis. Serial sections of the adrenals, however, reveal an advanced degenerative process (Fig. 1). The capsules are somewhat thickened. The architecture of the zona glomerulosa is irregularly distorted by what are apparently regenerating cells. The lipoid is present as finely granular particles in the degenerated areas, and is apparently reduced in amount. These are smaller, darker, polymorphic cells with homogeneous cytoplasm and do not exhibit the normal radial arrangement. The cells of the zona fasciculata are greatly enlarged and show marked vacuolar degeneration (Fig. 2). This degeneration can be traced through various stages to complete necrosis and eventual disappearance of the cells. The necrosis becomes more marked as the medulla is approached. Due to the absorption of large numbers of these cells, groups of enlarged, vacuolated cells are separated by apparently thickened reticulum, giving these portions of the cortex a gland-like appearance. In the right adrenal, intact medullary tissue cannot be found. In large areas it is completely necrotic, while in others only the reticulum is visible. Well-preserved areas of medullary tissue, however, are to be seen in the left adrenal. Marked hyperemia and numerous diffuse capillary and small venous thromboses are present. Especially in the zona reticulata and medulla are found many small hemorrhages and large amounts of hemosiderin pigment, mostly extracellular (Fig. 3). Focal collections of round cells are scanty. A moderate edema of the interstitial tissue is also present.

Anatomical Diagnosis. Cachexia with complete loss of adipose tissue and atrophy of the internal organs; decubitus ulcers over sacrum, elbows and ilia; chronic adhesive pleuritis; bronchopneumonia; dilatation of right heart; chronic perihepatitis, pericholecystitis and perisplenitis; congestion of liver; acute splenitis; arteriosclerotic nephritis; degeneration of adrenal glands.

Discussion. Unquestionably, on admission, our case was one of malnutritional edema. The history of inanition, the absence of other etiologic factors in the causation of edema both clinically and at autopsy and the spectacular response to a high caloric, vitamin B-rich diet admit of no other interpretation. This syndrome, moreover, has become so well known since the hunger blockade of the Great War and the post-war famines, that it needs no further comment here.

The puzzling feature of our case is the fact that in spite of the continuation of his diet and for no reason that could be demonstrated by clinical and laboratory examinations, the patient, in the second half of his illness, suddenly began the progressive deterioration previously described. The outstanding features were *the complete loss of body fat and an advanced degenerative lesion of both adrenals* with necrosis, regeneration, hemorrhages and capillary and venous thromboses.

Although this galaxy of symptoms is strongly reminiscent of

Addison's disease, the large number of atypical features present make this diagnosis untenable. While either the absence of pigmentation, gastro-intestinal disturbances, low blood pressure or practically complete destruction of the adrenal cortices can occasionally be present as individual aberrations from the typical syndrome, their combined absence in a single case militates strongly against such an assumption. *An additional differential point is the complete absence of body fat.* That loss of weight, often quite pronounced, occurs in the vast majority of cases of Addison's disease is well known. However, it never leads to marked cachexia, unless influenced by some such underlying disease as cancer. In most cases, it is moderate in degree and a definite adipose layer is present in the abdominal wall and in the abdomen.[1]

There are two other diseases, pituitary cachexia and multiple endocrine gland sclerosis, which bear some resemblance to the case under discussion. Both, however, run an exquisitely chronic course. In the former, the emaciation is accompanied by wrinkling of the skin, falling out of the hair and teeth and at autopsy, a lesion of the pituitary gland is demonstrable. In the latter, there is grafted on the pituitary cachexia, symptoms of both myxedema and adrenal insufficiency.

The condition, we believe, forcibly suggests the state of chronic adrenal insufficiency in animals produced by bilateral suprarenalectomy described by Marine and Baumann[2] and by Jaffe.[3] Jaffe summarizes the symptoms as follows: progressive emaciation with marked or complete loss of body fat, asthenia and liability to snuffles and skin infections. The most striking phenomenon is the disappearance of the fat, which may be complete in animals with insufficiency of long standing.

The effect of inanition and the various vitamin deficiencies on the adrenal glands has long been a matter of great interest. Jackson,[4] who has exhaustively reviewed and analyzed the literature up to 1923, made the following digest: In the human adult during total inanition there is an increase in the size of the adrenals in most cases. In animals, it is usually very marked. Notable enlargement also occurs in partial inanition, especially in malnutritional edema. The enlargement appears to be due in some cases to an hypertrophy of the cortex, in others of the medulla or of both. There is a congestion of the bloodvessels and sometimes hemorrhage. A variable degree of cell atrophy is present. The behavior of the lipoid and pigment is variable, although the latter is frequently increased. In the medulla, the changes are less marked and less frequent than in the cortex.

A review of recent experimental work reveals that it is still a moot question both as to whether these changes are due to inanition or B-avitaminosis and as to what portion of the gland is affected. Some investigators attribute them specifically to a lack of vitamin B,[5]

others to both inanition and vitamin B deficiency,[6] while still others claim that the hypertrophy is less marked in inanition.[7] The difficulty of differentiating between the effects of inanition and vitamin B deficiency is still further complicated by the apparent multiplicity of the latter. The hypertrophy in vitamin-B deficient pigeons, according to Marrian *et al.*,[8] is due mainly to B^1, but B^2 is a contributory factor. Findlay[9] found that it occurred in rats lacking either B^1 or B^2. The confusion is just as marked with regard to the location of the hypertrophy. Recently, it has been hypothesized that with starvation, there is an hypertrophy of the medulla, and with vitamin B deficiency, of the cortex.[10] The microscopic changes have received scant investigation.

It is obvious that the adrenal changes described, both in the human adult and the experimental animal, do not represent a true hypertrophy. The increase in weight of the adrenals is due to congestion, hemorrhage, and regeneration. Marrian[10] found a 19 per cent increase in the water content of the adrenals of pigeons on vitmin B-deficient diets and a 44 per cent increase after starvation.

It is conceivable that the degenerative lesions in the cortex, medulla or both could occasionally outweigh these factors and produce normal sized or even shrunken adrenals, thus accounting for some of the discordant results.

The alterations in structure must manifestly affect the functions of the gland, though experimental and clinical data appertaining to this question are meager. McCarrison[11] has reported changes in the adrenalin content of the suprarenals of animals fed on a variety of deficient diets. Peiser[12] compared the adrenalin content of the suprarenals secured at autopsy from subjects dying during the hunger blackade with those before the war, and found it to be two-thirds of the pre-war amount. Sehrt[13] has called attention to the ineffectiveness of the adrenalin extracted from animal adrenals during the blockade.

In human malnutrition, the significance of the changes in size, structure and function of the adrenals and the clinical symptoms they produce, if any, are unknown. We have been able to find but two observations bearing on this question. In reviewing his extensive experience with malnutritional edema, Tallqvist[14] states that the symptoms indicate both thyroid and adrenal insufficiency. Enright[15] has reported 54 cases of malnutritional edema in which the outstanding features at autopsy were a complete loss of body fat and shrunken adrenals. These cases closely approximate the one under discussion, but, unfortunately, all of them were associated with some other disease, usually pellagra. He considers the clinical picture to be due to a combination of debilitating disease and food deficiency operating to produce an adrenal insufficiency.

The uncomplicated chain of events in our patient, in conjunction with the findings at autopsy, establishes, we believe, not only a con-

nection between malnutritional edema and adrenal degeneration but a clinical syndrome of chronic adrenal insufficiency which closely resembles that state in the experimental animal. The conception of a relationship between malnutrition and adrenal changes is supported by a wealth of clinical and experimental observations and, moreover, is not unique; as another nutritional disturbance, rickets, is frequently associated with lesions of the parathyroid glands. In fact, Wells[16] has suggested a dietary imbalance as a possible factor in idiopathic adrenal atrophy. Exact proof, however, of the causal relationship between the morphologic findings in the adrenals and the clinical symptoms exhibited by the patient must await a quantitative measure of adrenal function and a reliable substitution therapy.

Summary. 1. A case of malnutritional edema is reported which exhibited an unusual clinical syndrome and a degenerative lesion of the adrenals at autopsy.

2. The outstanding clinical features were extreme emaciation with complete loss of body fat, asthenia, anorexia, polyneuritis, trophic ulcers and absence of pigmentation and hypotension.

3. The similarity between the syndrome and the state of chronic adrenal insufficiency in animals produced by bilateral suprarenalectomy is pointed out.

4. The literature on the effect of total and partial inanition and the various vitamin deficiencies on the adrenal glands in both animals and man is reviewed.

5. It is suggested that this clinical syndrome, hitherto undescribed, is one of chronic adrenal insufficiency due to the adrenal degeneration occasioned by malnutrition.

We have recently observed a case of malnutritional edema in an Italian male, aged 53 years, who presented the same syndrome as that described above, with certain exceptions. The edema was not as pronounced. The course was more rapid, and the loss of subcutaneous fat, though extreme, had not reached a total disappearance. At autopsy, the right adrenal was completely absent except for a few shreds of tissue, which on microscopic examination showed the typical changes described in idiopathic adrenal atrophy. The left adrenal was markedly hypertrophied, weighing 12.8 gm., and microscopic examination showed a degenerative process similar to but much less advanced than that in the first case.

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HYPERMOTILITY OF THE GASTRO-INTESTINAL TRACT IN HYPERTHYROIDISM.

A Study of 42 Cases.

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Hypermotility of the gastro-intestinal tract in hyperthyroidism has received little or no mention in the literature, although this is a prominent symptom in many patients with thyroid disease. Hence, a series of 42 patients with thyroid disease were studied at the Cleveland Clinic. These patients were examined before operation and again 7 to 10 days after thyroidectomy. The studies were made with the regular barium meal used for investigation of the gastro-intestinal tract. Fluoroscopic examinations were made at the time of ingestion of the meal, and 3 hours later roentgenograms were made to locate the head of the barium meal.

Hurst[1] suggested an average rate or time table for the "head" of the ingested meal as follows: cecum, 4 hours; hepatic flexure, 6 hours; splenic flexure, 9 hours; pelvic colon (sigmoid), 12 hours.

Béclère and Meriel,[2] and others, have stated that after ½ hour the opaque meal may be seen on the left and in the midabdomen. After 2 hours it usually is found in the middle and lower abdomen. After 4 hours it occupies only a portion of the ileum and is already manifest in the cecum. At 6 hours only a little remains in the terminal ileum. At the end of 8 hours the small bowel is completely empty. The investigations of Hurst showed that after a barium test meal the shadow of the cecum began to appear 4⅜ hours after ingestion. He computed the rate at which the intestinal contents travel as about 2.5 cm. per minute. Carman[3] stated that at the end of 6 hours, when the stomach is empty and the head of the meal is found between the cecum and the hepatic flexure,

the gastro-intestinal motility is considered to be normal. This is true if there is no deviation from the normal of other factors, such as acidity, peristalsis, tonus and pyloric function. Further, he added that a degree of hypermotility, as evidenced by advancement of the meal beyond the hepatic flexure and by the rapid discharge of the second meal through the pylorus, not rarely has a physiologic explanation, such as, for example, the presence of a hypertonic steer-horn stomach. But he felt that roentgenologic evidence of marked hypermotility should stimulate a search for possible causes. In the presence of a decided hypermotility Carman stated that duodenal ulcer, gastric carcinoma, anacidity and diarrhea should be considered as possible causes. He made no mention of hyperthyroidism.

Examination of patients with hypothyroidism by Warfield[4] showed ptosis of the stomach with retention of the barium meal in the descending colon and sigmoid for from 56 to 72 hours.

Wohl[5] recently reported observation in patients with hypothyroidism who showed marked hypomotility in the gastro-intestinal tract. He summarized the part played by the autonomic nervous system as follows: Vagotonia supposedly is associated with hypermotility, increased peristalsis and increased gastric secretion. The nerves of the sympathetic group produce the opposite or inhibiting effect on the gastro-intestinal canal and are presumed to be responsible for delayed emptying of the stomach, the diminished gastric secretions and also diminished gastric peristalsis. Eppinger and Hess[6] spoke of a balance between the vagus and sympathetic nervous systems which they believed was maintained by the effect of the secretions of the ductless glands on the whole autonomic nervous system.

The occurrence of hypermotility of the colon in 10 per cent and of stasis of the colon in 30 per cent of a series of cases with achlorhydria reported by Hitzrot[7] leaves some doubt as to Carman's suggestion regarding the part played by anacidity or achlorhydria in the production of gastric hypermotility.

The clinical significance of a study of gastro-intestinal hypermotility associated with thyroid disease is apparent when one considers the significance of digestion and absorption in the intestinal canal. Howell[8] pointed out that food undergoes its most profound digestive changes in the intestines, and that it is here also that the products of digestion are mainly absorbed. Intestinal digestion begins in the duodenum and is largely completed by the time that the food arrives at the ileocecal valve. Thus, in extreme hypermotility of the intestine, there is probably very great disturbance of the functions of digestion and absorption. An analysis of the cases studied is shown in Table 1.

If one uses Hurst's standard for the estimation of hypermotility,

it would be safe in stating that if the head of the meal in 3 hours is beyond the cecum, there is hypermotility of the gastro-intestinal canal. In analyzing this series of cases it was found that by the above criteria, 39 cases (92.8 per cent) manifested hypermotility of the gastro-intestinal tract before operation. In 2 cases (4.7 per cent) the head of the barium was in the cecum within 3 hours. In only 1 case (2.3 per cent) of the series was the barium in the small bowel, showing a normal motility at the end of 3 hours.

TABLE 1.

No.	Age.	Sex.	Wt. loss, lbs.	Head of barium before operation.	Head of barium after operation.	Bowel habits.	Operation.
1	21	F	24	Ascending colon	Hepatic flexure	Constipation	Posterior ligation.
2	50	F	20	Descending colon	Small bowel	Constipation	Thyroidectomy.
3	21	M	20	Rectum	Cecum	Irregular	Thyroidectomy.
4	33	F	39	Rectum	Splenic flexure	Diarrhea occ.	Thyroidectomy.
5	44	F	25	Small bowel	Cecum	Regular	Thyroidectomy.
6	57	F	28	Splenic flexure	Cecum	Constipation	Lobectomy.
7	29	F	25	Rectum	Cecum	Overactive	Thyroidectomy.
8	29	M	8	Splenic flexure	Cecum	Regular	Thyroidectomy.
9	35	F	25	Hepatic flexure	Small bowel	Regular	Thyroidectomy.
10	37	F	25	Splenic flexure	Ascending colon	Regular	Thyroidectomy.
11	41	F	58	Splenic flexure	Sigmoid	Constipation	Thyroidectomy (recurrent).
12	24	F	9½	Rectum	Small bowel	Regular	Thyroidectomy.
13	45	M	10	Transverse colon	Transverse colon	Normal	Thyroidectomy.
14	34	F	30	Transverse colon	Cecum	Constipation	Thyroidectomy.
15	25	F	30	Cecum	Small bowel	Constipation	Lobectomy.
16	35	M	13	Sigmoid colon	Descending colon	Constipation	Thyroidectomy.
17	31	M	38	Transverse colon	Rectum	Regular	Ligation.
18	40	F	40	Rectum	Rectum	Regular	Thyroidectomy.
19	21	F	6	Rectum	Transverse colon	Regular	Thyroidectomy.
20	12	F	0	Rectum	Rectum	Regular	Thyroidectomy.
21	50	F	19	Rectum	Hepatic flexure	Regular	Thyroidectomy.
22	21	F	0	Sigmoid flexure	Cecum	Regular	Thyroidectomy.
23	25	F	5	Splenic flexure	Descending colon	Constipation	Thyroidectomy.
24	38	F	20	Rectum	Hepatic flexure	Overactive	Thyroidectomy.
25	44	M	60	Rectum	Rectum	Ulcer. colitis	Lobectomy.
26	26	F	40	Hepatic flexure	Cecum	Constipation	Thyroidectomy.
27	44	F	20	Sigmoid	Transverse colon	Diarrhea occ.	Thyroidectomy.
28	52	F	21	Cecum	Hepatic flexure	Constipation	Thyroidectomy.
29	41	F	0	Rectum	Splenic flexure	Constipation	Thyroidectomy.
30	54	F	46	Rectum	Ascending colon	Regular	Lobectomy.
31	51	F	12	Splenic flexure	Cecum	Constipation	Thyroidectomy (recurrent).
32	46	F	25	Hepatic flexure	Cecum	Regular	Thyroidectomy.
33	52	F	12	Hepatic flexure	Cecum	Regular	Thyroidectomy.
34	50	F	4	Splenic flexure	Transverse colon	Regular	Thyroidectomy.
35	18	F	19	Rectum	Hepatic flexure	Regular	Thyroidectomy.
36	34	F	12	Sigmoid colon	Hepatic flexure	Regular	Thyroidectomy.
37	23	F	0	Splenic flexure	Cecum	Diarrhea	Thyroidectomy.
38	41	F	42	Splenic flexure	Cecum	Constipation	Thyroidectomy.
39	43	M	4	Sigmoid	Cecum	Regular	Thyroidectomy.
40	27	F	0	Sigmoid	Ascending colon	Regular	Thyroidectomy.
41	46	F	29	Splenic flexure	Ascending colon	Regular	Thyroidectomy.
42	22	F	25	Rectum	Splenic flexure	Regular	Thyroidectomy.

The analysis of the motility after operation is rather difficult to present because, by percentage statistics the true significance of the results obtained is not elicited. Figure 1 illustrates the position of the head of the meal in the 42 cases both before and after operation on the thyroid gland. The solid dot represents the position preoperatively and the solid triangles the position postoperatively.

It shows that in most instances before operation the site of the barium meal was beyond the mid-colon and that after operation in most cases it was located to the right of the mid-colon.

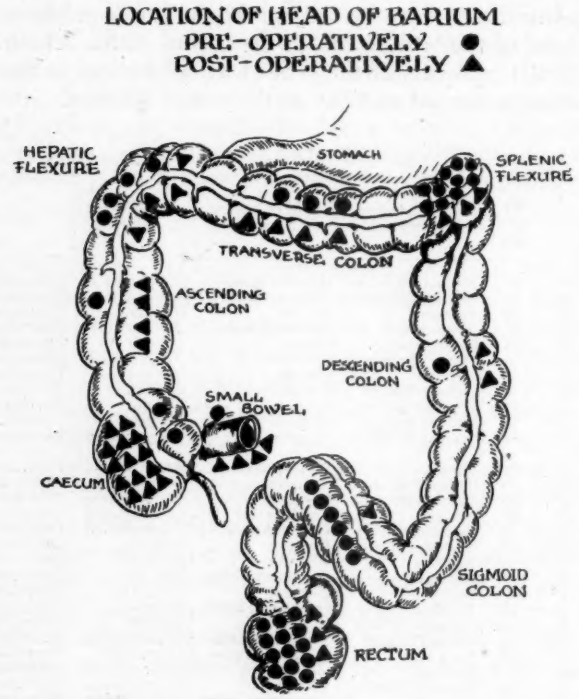

FIG. 1.—Schematic drawing, showing location of head of barium meal before and after thyroid operations.

Table 2 indicates the changes which took place in the location of the barium meal after operation.

TABLE 2.—CHANGES IN THE LOCATION OF THE BARIUM MEAL AFTER THYROIDECTOMY.

	Motility.		
	Unchanged.	Increased.	Decreased.
Head of barium:			
Rectum	3	0	11
Sigmoid	0	1	6
Descending colon	0	0	1
Splenic flexure	0	1	8
Transverse colon	1	1	1
Hepatic flexure	0	0	4
Ascending colon	0	1	0
Cecum	0	1	0
Small bowel	0	1	0
Total cases	4	6	32
Per cent	9.54	14.27	76.19

FIG. 2a FIG. 2b

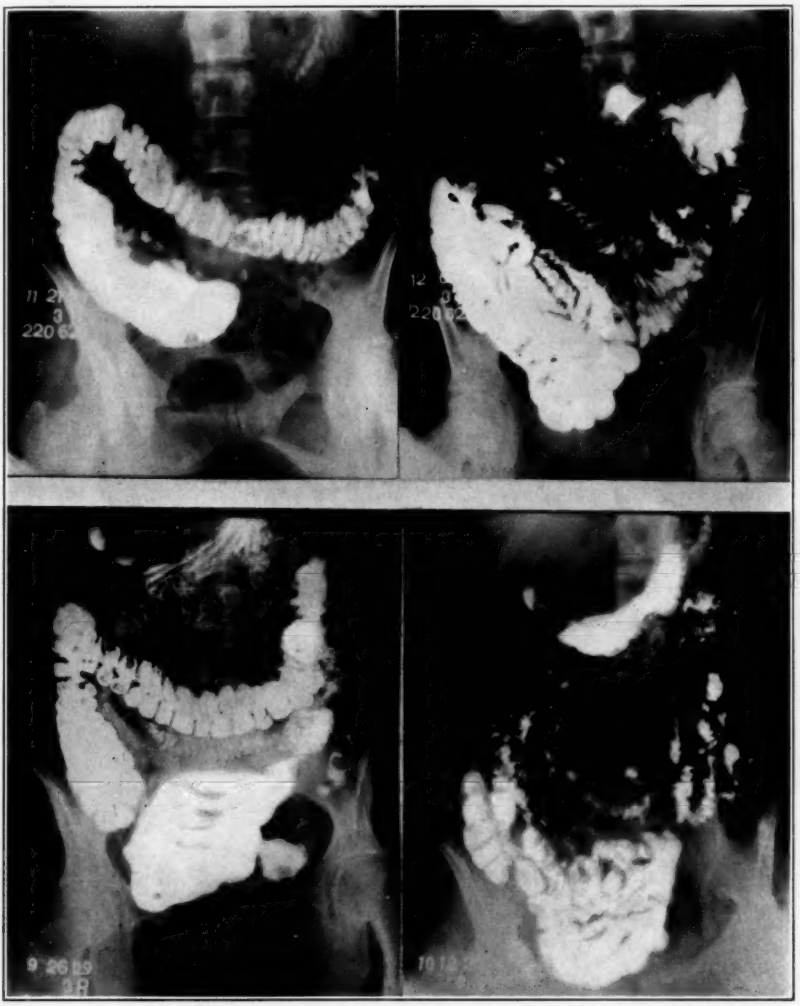

FIG. 3a FIG. 3b

FIG. 2.—(*a*) Before operation. (*b*) Nine days after thyroidectomy.
FIG. 3.—(*a*) Roentgenogram of colon before operation. (*b*) Roentgenogram of colon 5 days after thyroidectomy.

FIG. 4a FIG. 4b

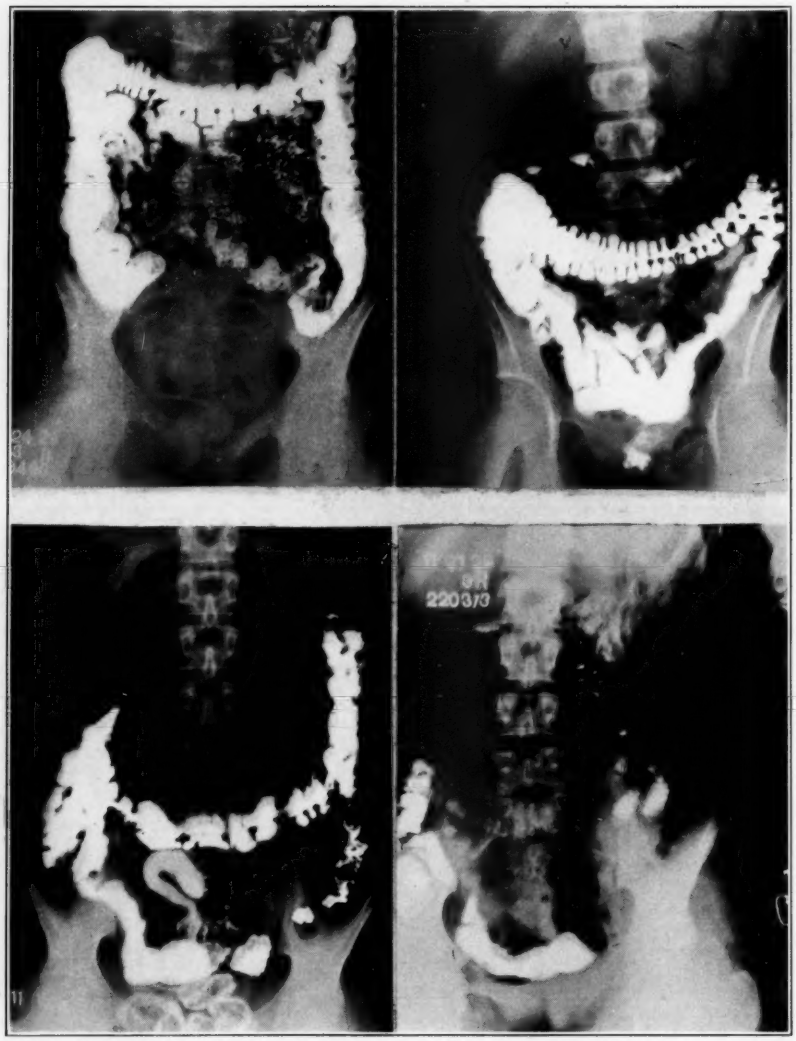

FIG. 5a FIG. 5b

FIG. 4.—(*a*) Roentgenogram of colon before operation. (*b*) Roentgenogram of colon 9 days after thyroidectomy.

FIG. 5.—(*a*) Roentgenogram of colon before operation. (*b*) Roentgenogram of colon 6 days after thyroidectomy.

The striking point in this analysis is the apparent change in the gastric motility which follows the clinical control of the hyperthyroidism. It would not be too much to say that these results show that there was some general systemic alteration following the removal of the thyroid.

The fact that there were 6 cases in which the intestinal motility was increased following operation is very interesting. One of these patients was subjected to bilateral ligation of the superior thyroid arteries, from which operation could not be expected such rapid clinical improvement as that following removal of the gland. Another of these patients in whom gastro-intestinal motility increased following operation was a child, aged 12 years, who was moderately active. In the group of cases in which there was no change after operation, 1 patient had chronic ulcerative colitis which persisted and probably had much to do with the hypermotility. The others offered no clinical evidence after the operation on the thyroid to account for persistence of an increased rate of movement in the gastro-intestinal tract.

The group in which there was a definite decrease in the motility following operation on the thyroid included 32 cases (76.19 per cent). This figure becomes even more significant when the degree of retardation in the hypermotility is analyzed. Table 3 shows the amount of retardation of movement calculated by comparison with the location of the barium meal before operation.

TABLE 3.—AMOUNT OF CHANGE IN GASTRO-INTESTINAL MOTILITY FOLLOWING OPERATION ON THE THYROID GLAND.

	Pre-operative location.	Slowed.	Per cent slowed.
Rectum	14	11	78.50
Sigmoid	6	6	100.00
Descending colon	1	1	100.00
Splenic flexure	10	8	80.00
Transverse colon	3	1	33.33
Hepatic flexure	4	4	100.00
Ascending colon	1	0	
Cecum	2	0	
Small bowel	1	0	

The following illustrations are from roentgenograms made on the same patients 3 hours after ingestion of the barium meal both before and after thyroid operation (Figs. 2 and 3).

In analyzing the bowel habits of the patients in this series it was found that 13 patients (30.9 per cent) were constipated, 6 patients (14.2 per cent) had diarrhea and 23 patients (54.8 per cent) had regular bowel movements.

In the cases with diarrhea 1 patient had chronic ulcerative colitis which accounted entirely for this finding. The others, however, were patients with uncomplicated hyperthyroidism.

It was possible in 12 cases to study the gastric secretions by means of the Rehfuss fractional test meal. In these 12 cases all but 2 patients showed a very marked hypermotility of the gastro-intestinal canal. Free hydrochloric acid and total acid was found to be low in 5 cases (41.6 per cent). Free hydrochloric acid was absent in 6 cases (50 per cent), and there was normal free hydrochloric acid in 1 case (8.4 per cent).

The most important clinical finding that this problem has educed is the association of the finding of low serum protein in cases of hyperthyroidism. This will be reported in a later paper. But it seems apparent that in the short time required for passage of the barium through the digestive canal, as demonstrated by these observations, it would be rather difficult for a patient with severe hyperthyroidism having marked hypermotility of the gastro-intestinal tract to assimilate the ingested foods completely. The fact that the barium meal reaches the rectum within 3 hours indicates that food is retained for a very short period in the small intestine, the area of greatest absorption. The exact amount of decrease in the absorption of foods is a problem to be worked out. But certainly in view of the rapid passage of ingested material through the bowel one can only conjecture that there would be decreased assimilation brought about by the hypermotility of the gastro-intestinal canal.

Summary.—1. The study of a series of 42 patients with hyperthyroidism showed that hypermotility of the gastro-intestinal canal occurs in this condition but that the degree of hypermotility is not an index to the severity of the disease.

2. Hypermotility of the gastro-intestinal tract was decreased, usually markedly, after removal of the thyroid in 76 per cent of the cases studied.

3. Hypermotility and anacidity occurred concomitantly in 12 cases of hyperthyroidism in this series.

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THE CORROBORATIVE VALUE OF AN IMPROVED GASTRO-DUODENAL BRAID IN THE DIAGNOSIS OF PEPTIC ULCER.

A Comparative Study of One Hundred Cases.

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The diagnosis of some diseases of the gastro-intestinal tract is at times so baffling that it taxes the ingenuity of the most experienced. No individual test, no matter how trivial, can be considered superfluous in corroborating the more important data at hand, and so aid in arriving at a final diagnosis.

For instance, in the diagnosis of peptic ulcer a good history is highly suggestive, the roentgenologic evidence is usually conclusive. Yet certain types of cases are encountered where either the history is atypical, the roentgenologic findings are insufficient and the laboratory data inconclusive. There is still another group of patients which displays a typical duodenal ulcer syndrome and proves to be normal roentgenologically, insofar as our criteria for diagnosing peptic ulcer is concerned. Such cases I have reported in a recent communication,[1] where I suggested that these cases be designated under the name of "subacute recurrent duodenitis." In this condition the history strongly suggests duodenal ulcer. Upon Roentgen ray examination, however, no evidence of ulcer can be found. The duodenal bulb appears hazy, displays signs of marked irritability, with rapid emptying. In view of such evidence one is reluctant in venturing a positive diagnosis of ulcer, and is compelled to resort to further search.

Other conditions frequently offering difficulties in diagnosis are periduodenal adhesions, either caused by disease in an adjacent organ, such as the gall bladder, or distortion of the duodenal bulb, as a result of scarring produced by a healed ulcer. Determining whether an ulcer is active or not, in the absence of definite symptoms, is also frequently a difficult point to decide by means of Roentgen ray evidence alone.

The purpose of this paper is to report on the diagnostic value of a gastroduodenal braid, which was first described by Cash[2] in 1923. This braid is actually a modification of the silk string and duodenal bucket described by Einhorn[3] in 1909. It has very distinct advantages over the Einhorn string, and these I will soon mention. The Cash braid (Fig. 1) consists of a proximal and a distal portion. The proximal portion is loosely knitted, tubular silk braid, $\frac{1}{2}$ inch in diameter, about 13 inches in length, and is white, flexible and

compressible. The distal portion which is attached to the proximal, is a twisted No. 15 silk string 17 inches long, having a knot 4 inches from its distal end, indicating the lip mark. The entire length of the braid available for swallowing is about 26 inches.

The braid is swallowed before retiring, several hours after the evening meal, and is allowed to remain over night. The patient is

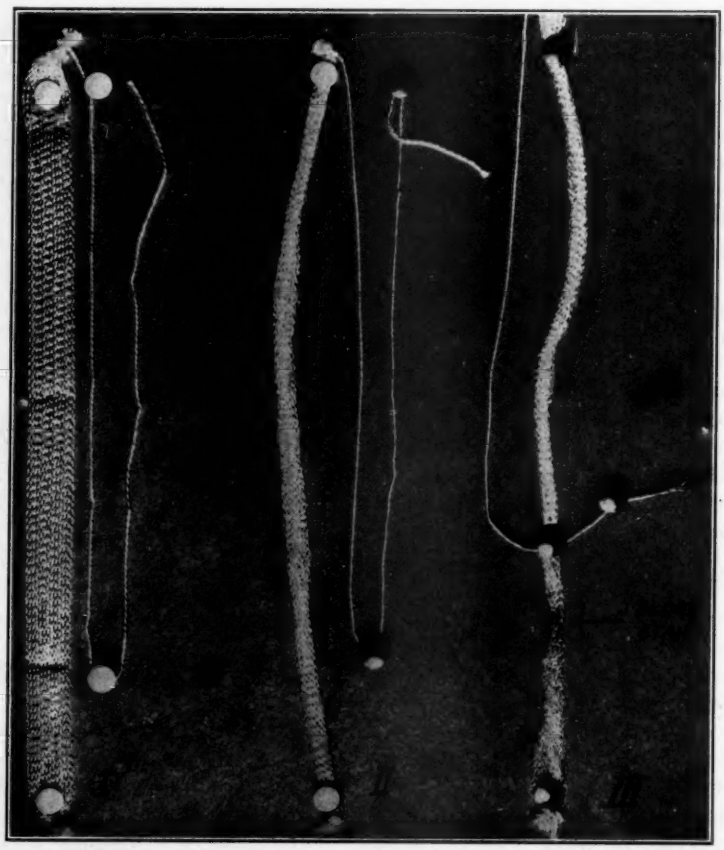

FIG. 1.—Showing the modified gastroduodenal braid. *I*, appearance of the braid before it is swallowed; *II*, appearance of the braid after remaining in the gastroduodenal tract overnight; *III*, demonstration of a localized blood stain in an ulcer case.

instructed not to partake of any food or beverage which may color the braid. The distal 4 inches of the braid are affixed to the cheek by a piece of adhesive plaster to prevent swallowing of entire braid during sleep.

The advantages of this braid are quite obvious. It offers a large surface for contact with the ulcer area, producing usually a

very definite blood stain. Because of its compressibility the compression or narrowing produced on the braid by the pyloric sphincter can be easily made out, thus localizing this part of the stomach and thereby the lesion, whether gastric or duodenal. Bile stains can also be readily detected, and are at times invaluable evidence of a chronic duodenal obstruction or duodenal dilatation, as our observations compared with roentgenologic findings have definitely shown in many cases. The size and texture of this braid is such that prevents abrading of the gastroduodenal mucosa, as frequently may be the case when using an ordinary string, in an irritable stomach with a sensitive, hyperemic mucosa.

One learns by experience that only an isolated localized stain is pathognomonic of ulcer. Diffuse staining of the braid is usually caused by bleeding from the gums or throat; rarely by the braid coming in contact with a hyperemic mucosa. In gastric malignancies the stain is frequently diffuse, though rather distinctly deep in color. Food may at times color the braid, but one can easily distinguish the type of stain.

This study comprises a series of 100 cases (95 hospital and 5 private) on whom complete roentgenologic studies of the gastrointestinal tract have been made, always preceded by the necessary examinations and administration of the braid. In some suspicious cases 2 or 3 braids had to be administered in order to arrive at a definite conclusion. The braid observations have been checked with the roentgenologic reports with reference to two findings: (1) Blood stain, indicating peptic ulcer, and (2) a deeply colored bile stain which we have learned to denote duodenal dilatation or chronic duodenal obstruction. (See Tables 1 and 2.)

TABLE 1.—RELATION OF BRAID TO ROENTGEN RAY FINDINGS AND HISTORY IN ULCER DIAGNOSIS.

	Braid stain.	Ulcer by Roentgen ray.	History.	Cases.
A	Negative	Negative	Nonsuggestive	45
B	Negative	Negative	Suggestive	10
C	Positive	Positive	Nonsuggestive	9
D	Positive	Positive	Suggestive	15
E	Positive	Negative	Nonsuggestive	11
F	Positive	Negative	Suggestive	2
G	Negative	Positive	Nonsuggestive	3
H*	Negative	Positive	Suggestive	5

* 2 of these found positive at operation.

TABLE 2.—RELATION OF BRAID TO ROENTGEN RAY FINDINGS IN DIAGNOSIS OF DUODENAL DILATATION.

	Bile stain.	Duodenal dilatation.	Cases.
A	Present	Found	32
B	Present	None found	4
C	Absent	Found	23
D	Absent	None found	41

Results and Comment. As will be seen from Table 1, of the 100 cases studied, 32 were diagnosed roentgenologically as peptic ulcer (24 duodenal and 8 gastric). Five additional cases were diagnosed by Roentgen ray as doubtful cases of ulcer, and the braid was negative for blood stain in each instance. These cases were not included in our ulcer group, although they lend additional evidence to the corroborative value of the braid in the diagnosis of peptic ulcer.

Ten of the 100 cases came to operation, 3 of which were diagnosed as ulcers by Roentgen ray and by the braid test and corroborated at operation. In 2 cases the Roentgen ray evidence seemed to favor a diagnosis of duodenal ulcer, the braid showed no evidence of blood stain, and no ulcers were found at operation. The remaining 5 cases were miscellaneous surgical entities, our pre-operative diagnoses being corroborated at operation.

Of the 32 cases diagnosed roentgenologically as ulcer, 24 (75 per cent) showed a definite, localized blood stain on the braid. Of the remaining 8 cases which failed to show braid evidence of ulcer as compared with Roentgen ray diagnosis, 2 cases subsequently were proven to be ulcers at operation. We are thoroughly convinced that although the above incidence of blood positive braids may appear high, yet similar results may be obtained in any group of suspicious ulcer cases, providing thorough search for blood stain is made, and the braid test repeated two or three times, if such procedure is warranted.

Ulcer History in Comparison to Blood Stain. It was interesting in this study to compare the history, in the group of ulcer cases with the braid and Roentgen ray findings, in view of the fact that the history is so typical in a good many ulcer patients. In Table 1 we find that of the 32 Roentgen ray positive cases, 20 (62.5 per cent) gave a suggestive ulcer history. Of the remaining 12 with a non-suggestive history, 9 cases (75 per cent) showed a positive blood stain on the braid, indicating a probable gastric or duodenal lesion. This again indicates the superiority of the braid evidence over the history. In 5 of the cases (15.6 per cent) the history and Roentgen ray findings were positive, although the braid showed no evidence of any blood stain. Comparing then the history with the braid findings, we obtained 62.5 per cent positive histories as against 75 per cent positive blood stained braids, in the entire group of ulcer cases.

Braid Evidence of Duodenal Dilatation. In 55 of our 100 cases, the Roentgen ray examination revealed some degree of dilatation of some portion of the duodenum—rather a high incidence. Of these, 32 (58.1 per cent) were diagnosed by the braid as having some form of duodenal stasis, as manifested by a deep, diffuse, golden, dark yellowish or greenish discoloration of the distal 2 or 3 inches of the braid. As before mentioned, we have come to recognize this finding as being indicative of a duodenal stasis in quite a large proportion

of cases. The doubtful cases of bile stained braids were not included in this group.

In 4 cases the braid showed a definite bile stain, although our roentgenologist was unable to confirm the findings of duodenal abnormality. In 23 patients the Roentgen ray showed evidence of duodenal dilatation, while the braid findings were negative. As to whether the findings of duodenal dilatation in our group of cases were responsible for symptoms, we are at present not prepared to say. Undoubtedly in a certain proportion of cases the symptomatology may have been attributed to some degree of duodenal stasis.

Summary and Conclusions. The results of a comparative study of the corroborative diagnostic value of the gastroduodenal braid are herein reported. The advantages of the braid over the Einhorn string are described.

In a series of 100 cases in which a complete roentgenologic study of the gastro-intestinal tract has been made, followed by the administration of the braid, the braid results have been checked with the Roentgen ray findings with reference to two signs: (1) A localized blood stain, indicating a probable peptic ulcer, and (2) a deeply colored bile stain, which we learned to recognize as a sign of a possible doudenal stasis. The diagnostic value of a suggestive ulcer history has also been compared with the braid and Roentgen ray findings.

Of 100 cases studied, 32 were diagnosed roentgenologically as peptic ulcer (24 duodenal and 8 gastric). Five of these came to operation. Of the entire group of ulcer cases, 75 per cent have shown a definite blood stain on the braid, indicating ulcer. In 2 cases the braid was positive for blood, the Roentgen ray findings were negative, and ulcer was found at operation, while in 2 other cases which came to operation, the braid was negative, the Roentgen ray findings were positive, and ulcer was found at operation.

Comparing the history with the braid findings in the same group of cases, we obtained in 62.5 per cent of the patients histories that were suggestive of peptic ulcer, as against 75 per cent positive blood stained braids.

In 55 of the 100 cases the Roentgen ray examination revealed some degree of duodenal dilatation. Of these, 32 (58.1 per cent) were diagnosed by the gastroduodenal braid.

The results of this study readily demonstrate the value of the gastroduodenal braid as an adjunct in the diagnosis of peptic ulcer.

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SHORT INTERVAL OBSERVATIONS ON THE BLOOD IN PERNICIOUS ANEMIA AFTER NON-PURIFIED LIVER EXTRACT INTRAVENOUSLY.*

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In 1930 Gänsslen reported 100 cases of anemia treated successfully with intravenous liver extract therapy, of which more than 40 were pernicious anemia. Unfortunately he gave no description of the preparation injected. Schilling, using Gänsslen's extract, confirmed his results and reported a series of 10 more cases of pernicious anemia with adequate treatment. Others who have made effective intravenous liver extracts are Cohn, West and their respective collaborators, Castle and Taylor, and Aubertin and Voillemin.

As a remission can be produced *very promptly* by the injection of liver extract intravenously, it was decided to use this method to study the early changes in the blood with the onset of the reticulocyte response. This method has the advantage that the changes can be timed very carefully after the administration of a known amount of the substance, eliminating the uncertainties of absorption by the oral or intramuscular routes. The blood of the 2 cases reported here was observed at 4-hour intervals day and night for 11 days.

Material and Methods. The liver extract used in Patient 1 was prepared according to the method of Castle and Taylor.[1] Lilly's No. 343 was extracted with ether, dissolved in physiologic salt solution, boiled for 3 minutes, filtered and boiled for 2 more minutes. The dosage given was 0.1 gm. per kg. body weight, which in this patient amounted to 10 gm. of the liver extract. The total volume given was 80 cc.

The second patient was given an extract similar to the above. This patient received 6.5 gm. of Lilly's liver extract No. 343, in a 50 cc. aqueous solution.

* Presented before the Central Society for Clinical Research, November 20, 1931. See Abstract, J. Clin. Invest., 1932, **11**, 860.

The injections were given very slowly, at the rate of approximately 4 cc. per minute. Blood pressure observations were made before and at frequent intervals after the injection, until the pressure became stabilized at the pre-treatment level.

The blood counts were made according to the usual methods, using U. S. Bureau of Standards certified pipettes and counting chambers. The hemoglobin was estimated by the Leitz-Sahli apparatus (14 gm. = 100 per cent). Complete counts were made twice daily, at 8 A.M. and 8 P.M., and Wright stained cover-glass films (brilliant cresyl blue and plain) at 4-hour intervals, day and night. During the period of observation the patients remained in bed. Each patient was given a routine house diet with no liver or kidney.

Case Histories. CASE 1.—Mr. P. P., aged 47 years (second relapse), had been diagnosed as having pernicious anemia in 1926, the outstanding features at that time being pallor, ease of fatigue, tiredness, dyspnea, numbness and tingling of extremities, nausea and vomiting, and increasing constipation. The patient had been on liver diet for 1½ years and then discontinued it. He felt well until 1 month previous to the present study, at which time he had a complete relapse. Physical examination revealed an adult male, extremely pale, icteric scleræ, atrophic tongue and pitting edema of the ankles. On admission the red blood cell count was 1,570,000 per c.mm., hemoglobin 41 per cent (Sahli) and white blood cell count 5800 per c.mm. Gastric analysis following the intramuscular injection of 1 mg. of histamin hydrochlorid showed no free hydrochloric acid. The patient received 10 gm. of Lilly's liver extract made up in solution with 80 cc. of 0.8 per cent sodium chlorid solution.

CASE 2.—Mr. J. S., aged 68 years (first relapse), felt comparatively well until 5 months previous to the present study. Since then he has noted a very poor appetite associated with numbness and tingling of the extremities, edema of the ankles, dyspnea, palpitation, dizziness, weakness, ease of fatigue and pallor. There was a loss of 15 pounds in weight. Physical examination revealed an adult male subacutely ill, lemon tint of the skin, mucous membranes pale, scleræ icteric, tongue papillæ atrophic, vibratory sense diminished over the bones of the left leg. No free hydrochloric acid was present in the gastric contents following histamin hydrochlorid injection. On admission the red blood cell count was 1,100,000 per c.mm., and hemoglobin 22 per cent (Sahli) and white blood cell count 4900 per c.mm. The patient was given 6.5 gm. of Lilly's liver extract No. 343, made up in a solution of 50 cc. of distilled water.

A definite response to the therapy as evidenced by an increase in the reticulocyte percentage was noted at the end of 24 hours. The calculated reticulocyte percentage, based on a standard of 4 to 6 vials of Lilly's liver extract No. 343 by mouth would have been 20.4 and 34.4 per cent in Patients 1 and 2, respectively, and this peak would have been reached on the 7th or 8th day of therapy. According to the reports of Sturgis, Isaacs and Rennie,[2] and those of Minot, Murphy and Stetson,[3] this is a most satisfactory response. In Case 1 the expected response (20.4 per cent) was reached within 68 hours, and a maximum of 49.5 per cent in 108 hours. In Case 2 the expected response (34.4 per cent) was reached within 68 hours and a maximum of 52.8 per cent in 88 hours. The responses noted

are much more significant when one considers that only slightly more than 1 vial of Lilly's liver extract No. 343 was given, and this was made from 100 gm. of fresh liver, which amount has little or no therapeutic value when administered orally.

Two of the cases reported by Castle and Taylor with initial red blood cell counts of 980,000 and 1,490,000 per c.mm. had reticulocyte responses of 27.8 and 25.4 per cent, respectively. The calculated maximum reticulocyte responses were 34.6 and 22.3 per cent, respectively. In comparable cases of Sturgis and Riddle, 15 to 30 times the amounts which were given intravenously were necessary for oral administration to obtain equally good results. The importance of these responses has been judged according to the standards obtained from the work of Minot and his associates, who calculated their results from the data obtained in studying a group of cases with varying degrees of anemia. In comparison with these standards, the responses obtained in Patients 1 and 2 were more than satisfactory. However, if intravenous liver therapy is to be used, it seems highly probable that a new series of standards will have to be calculated.[4]

In addition to the magnitude and rate of change of the reticulocyte response, 4 hourly variations were also noted. On one occasion there was a 36 per cent difference in the reticulocyte count within a 24-hour period. This daily fluctuation was reported by Porter and Irving[5] and Riddle and Sturgis.[6] Apparently the variation is the result of some physiologic process which governs the metabolic activity of the bone marrow, but its significance may be questioned by a consideration of the factor of error in estimating the reticulocyte count. Inasmuch as the limit of error has not been determined, this factor remains an open question.

In Patient 1 there occurred an increase per c.mm. of 1,000,000 red blood cells in 10 days and 2,000,000 red blood cells in 15 days. In the same periods of time the hemoglobin percentage increased 24 per cent and 27 per cent above its original level. In Patient 2 there occurred an increase of 1,000,000 red blood cells within a 10-day period with a hemoglobin increase of 28 per cent (Tables 1 and 2). Similar data were also obtained in the case reports of Riddle and Sturgis and Porter and Irving.

A mild leukocytosis was observed in both cases at infrequent intervals during treatment. The temporary increase in the white blood cell count was reported by Riddle and Sturgis and was considered by them as a bone marrow stimulation phenomenon. Inasmuch as neither patient had any concomitant signs or symptoms of infection, the stimulation of the bone marrow undoubtedly accounts for the transient increase of the white blood cell count. Careful study of serial blood films showed a temporary increase in the peripheral circulation of all the elements of the marrow. The platelets were markedly increased in number with the presence of

TABLE 1.—SUMMARY OF BLOOD FINDINGS—PATIENT 1.

Date.		Red blood cell count.	White blood cell count.	Hemoglobin, per cent.	Reticulocyte count.	Hours of treatment.
May 25	. . . . .	1.57	5800	41	2.7	-24
26	. . . . .	1.43	2650	45	2.0	
26	2 P.M. . . .	1.59	2900	47	4.4	2
	8 P.M. . . .	1.40	1650	47	3.0	8
27	Midnight . .	..	..	..	3.2	12
	4 A.M. . . .	..	..	..	3.8	16
	8 A.M. . . .	1.40	7600	41	3.7	20
	NOON . . .	..	..	..	3.4	24
	4 P.M. . . .	..	..	..	4.7	28
	8 P.M. . . .	1.54	4300	39	5.0	32
28	Midnight . .	..	..	..	6.4	36
	4 A.M. . . .	..	..	..	3.7	40
	8 A.M. . . .	1.66	7400	51	6.7	44
	NOON . . .	..	..	..	11.8	48
	4 P.M. . . .	..	..	..	16.8	52
	8 P.M. . . .	1.79	6300	44	13.2	56
29	Midnight . .	..	..	..	16.7	60
	4 A.M. . . .	..	..	..	18.8	64
	8 A.M. . . .	1.93	8000	45	21.7	68
	NOON . . .	..	..	..	21.1	72
	4 P.M. . . .	..	..	..	25.8	76
	8 P.M. . . .	2.00	6450	51	28.2	80
30	Midnight . .	..	..	..	27.5	84
	4 A.M. . . .	..	..	..	38.9	88
	8 A.M. . . .	1.88	6300	48	38.0	92
	NOON . . .	..	..	..	42.6	96
	4 P.M. . . .	..	..	..	45.0	100
	8 P.M. . . .	1.87	4300	51	46.3	104
31	Midnight . .	..	..	..	49.5	108
	4 A.M. . . .	..	..	..	38.0	112
	8 A.M. . . .	1.96	8600	47	38.2	116
	NOON . . .	..	..	..	42.0	120
	4 P.M. . . .	..	..	..	25.5	124
	8 P.M. . . .	2.17	6400	51	31.4	128
June 1	Midnight . .	..	..	..	25.8	132
	4 A.M. . . .	..	..	..	26.4	136
	8 A.M. . . .	2.26	7650	49	35.3	140
	NOON . . .	..	..	..	27.4	144
	4 P.M. . . .	..	..	..	31.8	148
	8 P.M. . . .	2.87	4550	53	24.3	152
2	Midnight . .	..	..	..	20.0	156
	4 A.M. . . .	..	..	..	13.5	160
	8 A.M. . . .	2.90	7900	53	21.3	164
	NOON . . .	..	..	..	14.7	168
	4 P.M. . . .	..	..	..	..	172
	8 P.M. . . .	2.12	3450	53	12.5	176
June 3	Midnight . .	..	..	..	16.3	180
	4 A.M. . . .	..	..	..	9.6	184
	8 A.M. . . .	2.23	5850	57	16.9	188
	NOON . . .	..	..	..	12.3	192
	4 P.M. . . .	..	..	..	13.9	196
	8 P.M. . . .	2.13	4050	60	14.1	200
4	Midnight . .	..	..	..	11.7	204
	4 A.M. . . .	..	..	..	12.8	208
	8 A.M. . . .	2.61	8800	58	14.3	212
	NOON . . .	..	..	..	11.8	216
	4 P.M. . . .	..	..	..	16.5	220
	8 P.M. . . .	2.60	3300	65	12.6	224
5	Midnight . .	..	..	..	10.9	228
	4 A.M. . . .	..	..	..	11.3	232
	8 A.M. . . .	2.77	..	..	9.6	236
	NOON . . .	..	..	..	14.3	240
	4 P.M. . . .	..	..	..	9.9	244
6	8 A.M. . . .	2.68	9950	61	13.0	260
7	8 A.M. . . .	2.91	6000	66	7.8	284
8	8 A.M. . . .	3.73	10,000	69	3.9	308

TABLE 2.—SUMMARY OF BLOOD FINDINGS—PATIENT 2.

Date	Red blood cell count.	White blood cell count.	Hemoglobin, per cent.	Reticulocyte count.	Hours of treatment.
June 1	0.98	3,600	15	3.7	−24
2 3 P.M.	1.11	4,900	22	4.2	
4 P.M.	1.08	2,050	22	5.5	
8 P.M.	0.86	1,250	21	5.2	4
3 Midnight	..	..	..	5.1	8
4 A.M.	..	..	..	4.4	12
8 A.M.	0.94	5,100	20	6.7	16
NOON	..	..	..	4.4	20
4 P.M.	..	..	..	3.7	24
8 P.M.	0.75	3,950	19	7.2	28
4 Midnight	..	..	..	7.3	32
4 A.M.	..	..	..	9.5	36
8 A.M.	1.03	5,400	25	12.9	40
NOON	..	..	..	9.4	44
4 P.M.	0.76	7,800	21	9.0	48
8 P.M.	1.11	8,600	26	17.0	52
5 Midnight	..	..	..	12.7	56
4 A.M.	..	..	..	29.4	60
8 A.M.	1.16	13,500	28	31.0	64
NOON	..	..	..	32.7	68
4 P.M.	..	..	..	48.9	72
8 P.M.	1.02	6,000	27	..	76
6 Midnight	..	..	..	47.0	80
4 A.M.	..	..	..	39.4+	84
8 A.M.	1.23	6,100	29	52.9	88
NOON	..	..	..	49.5	92
4 P.M.	..	..	..	44.9+	96
8 P.M.	1.23	2,950	31	..	100
7 Midnight	..	..	..	29.4+	104
4 A.M.	..	..	..	49.0	108
8 A.M.	1.25	4,300	32	49.7	112
NOON	..	..	..	43.6	116
4 P.M.	..	..	..	..	120
8 P.M.	1.30	3,450	32	45.1+	124
8 Midnight	..	..	..	51.3	128
4 A.M.	..	..	..	46.9	132
8 A.M.	1 64	4,550	34	33.6	136
NOON	..	..	..	36.4	140
4 P.M.	..	..	..	41.5	144
8 P.M.	1.48	3,650	35	50.3+	148
9 Midnight	..	..	..	48.5	152
4 A.M.	..	..	..	43.3	156
8 A.M.	1.56	6,800	38	22.1	160
NOON	..	..	..	..	164
4 P.M.	..	..	..	39.1	168
8 P.M.	1.78	5,950	38	..	172
10 Midnight	..	..	..	..	176
4 A.M.	..	..	3	38.8	180
8 A.M.	1.99	10,700	42	29.3	184
NOON	..	..	..	35.0	188
4 P.M.	..	..	..	36.3	192
8 P.M.	1.43	6,550	43	21.1	196
11 Midnight	..	..	..	22.4	200
4 A.M.	..	..	..	13.6	204
8 A.M.	1.84	8,400	45	17.0	208
NOON	..	..	..	19.4	212
4 P.M.	..	..	..	9.6	216
8 P.M.	1.40	6,400	43	14.5	220
12 Midnight	..	..	..	15.0	224
4 A.M.	..	..	..	16.1	228
8 A.M.	1.89	8,050	45	11.6	232
NOON	..	..	..	15.5	236
4 P.M.	..	..	..	16.3	240
8 P.M.	1.73	5,800	44	14.6	244
13 Midnight	..	..	..	12.3	248
4 A.M.	..	..	..	9.3	252
8 A.M.	1.67	9,900	44	14.5	256
NOON	..	..	..	13.9	260
4 P.M.	..	..	..	9.2	264
8 P.M.	2.08	7,200	43	16.6	268
14 Midnight	..	..	..	12.6	271
4 A.M.	..	..	..	8.0	276
8 A.M.	2.22	7,200	49	7.8	280
NOON	..	..	..	12.0	284
4 P.M.	..	..	..	..	288
8 P.M.	1.92	5,950	47	..	292
15 Midnight	..	..	..	12.2	296
4 A.M.	..	..	..	6.0	300
8 A.M.	2.16	14,700	45	5.9	304
NOON	..	..	..	5.6	308
4 P.M.	..	..	..	7.0	312
8 P.M.	..	..	..	..	316

many giant forms; there was a "shift to the left" in the myeloid series with all types of cells being present in an increased amount; the red cells showed all forms of immaturity from blast cells through the various stages to mature cells. This crisis may be due to a clearing of the liver and spleen, which resume their fetal hemopoietic function during the relapse in severe cases of pernicious anemia, as well as to stimulation of the bone marrow.

Clinical Effects. The clinical effects noted in both patients were striking in their similarity. They may be classified into two groups: (*a*) The immediate effects as a result of the injection; (*b*) changes noted with clinical improvement following adequate therapy. The picture during and immediately following the injection is characteristic of a systemic reaction to histamin or cholin. The patients described a sensation of warmth over the entire body, especially the face. Accompanying this was a choking sensation, a feeling of air hunger or a sense of marked pressure over the chest. There was a throbbing sensation in the head, the face became flushed and large beads of perspiration were observed over the forehead and about the mouth. These symptoms were transient, apparently could be somewhat influenced by the rate of injection and disappeared entirely with cessation of the injection.

Within a period of 45 to 60 minutes, the patients were suddenly seized with a severe chill. The rigor lasted for 90 minutes in Patient 1 and 30 minutes in Patient 2, and slowly abated. The temperature gradually mounted to 104° F. in Patient 1 and 102° F. in Patient 2. Accompanying the chill, Patient 1 had a severe vomiting spell, became cyanotic and complained bitterly of numbness of his fingers and hands. Within 24 hours all these symptoms had disappeared.

From this period on the clinical improvement compared more than favorably with those patients who received small daily doses of liver extract orally. The usual increase of appetite, strength and sense of wellbeing, as well as the decrease of pallor and icterus, took place much more rapidly with the intravenous therapy. With the oral administration of liver extract, the clinical improvement is usually seen in 72 to 96 hours. The 2 patients who received the extract intravenously showed evidence of clinical improvement within 48 hours.

Perhaps the most striking effect with the above intravenous preparations is the immediate lowering of the blood pressure, a phenomenon pointed out by Cohn, Minot and their associates, and Castle and Taylor. In Patient 1, 1 cc. of 1 to 1000 solution of adrenalin was given hypodermically 10 minutes before the intravenous therapy in order to counteract this depressor substance. Apparently it had no effect, the blood pressure falling from 155 to 90 systolic and from 85 to 50 diastolic, within 3 hours. The diastolic pressure returned to normal in 3 hours, whereas the systolic pressure re-

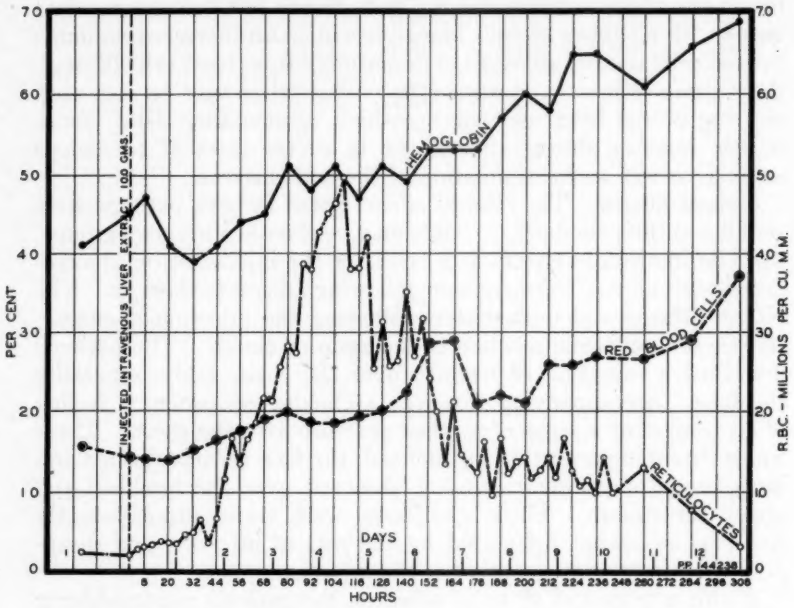

CHART I.—Response to single injection of liver extract intravenously (unrefined).

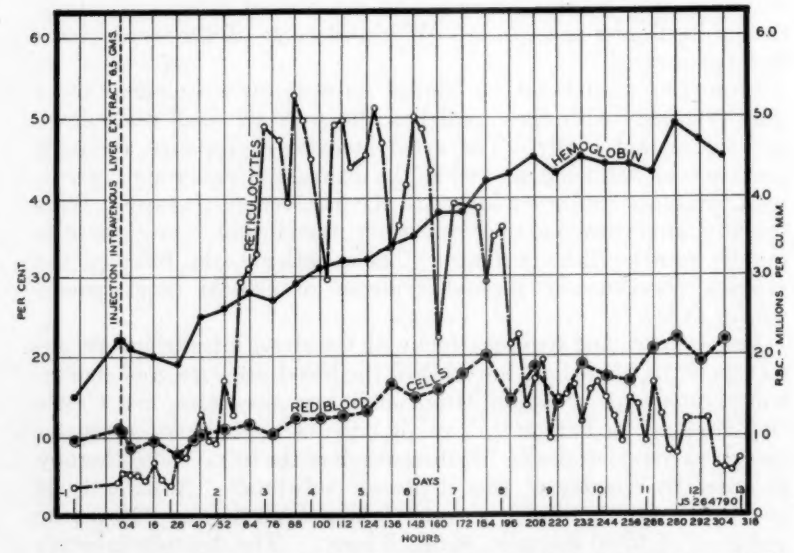

CHART II.—Response to single injection of liver extract intravenously (unrefined).

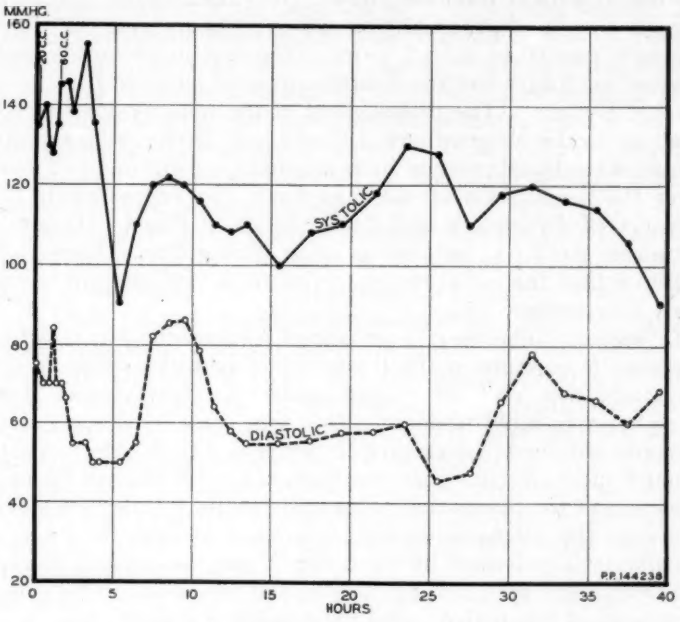

CHART III.—Blood pressure following intravenous injection of liver extract (unrefined).

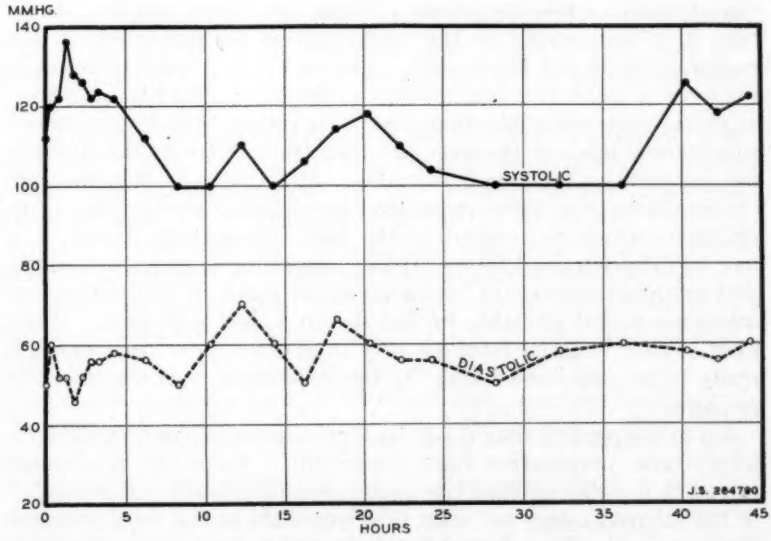

CHART IV.—Blood pressure following intravenous injection of liver extract (unrefined).

mained at a lower level for 2 days. In Patient 2 the systolic pressure was reduced from 120 to 100 in 8 hours and the diastolic pressure from 60 to 46 in 2 hours. The systolic pressure remained lowered for 2 days and the diastolic pressure returned to its original level in 8 hours. The prolongation of the hypotensive effect is in contrast to the observations of Castle and Taylor, who reported a return of the blood pressure to its original level within 1 to 2 minutes after the termination of the injection. The course of the blood pressure of Patients 1 and 2 are shown in Charts III and IV. Although the blood pressure is lower during sleep,[7] there is little question that the initial drop was due to the injection of the unrefined liver extract.

Discussion. The use of liver extract intravenously as an effective therapeutic measure in the treatment of pernicious anemia brings up many new and interesting problems. Intravenous therapy causes a more rapid response with a much smaller dosage, and the response obtained, if measured in terms of reticulocyte percentage, is much more effective than any form of liver treatment by mouth. If we accept the theory that pernicious anemia is a deficiency disease and that the substance lacking is present in both liver and ventriculin, or is generated by the latter, it may be possible to explain the mechanism by which the various substances act in the effective treatment of this malady, and their speed of action.

Food entering the gastro-intestinal tract is broken down into its various components, one of which is the unknown antianemic substance. This product or its precursors is probably formed in the stomach, since its presence there has been proven. From here it is transported to the bone marrow for utilization in the manufacture of red blood cells. The excess is probably stored in the liver[8] in much the same manner as glycogen. Such a hypothesis is much more plausible than the assumption that the unknown substance is made in the liver and then transmitted to the stomach for secretion or further distribution. It is just one step more to the conclusion that intravenous liver preparations contain the active principle, which is supplied to the body through the blood, in a free and concentrated form. If this same liver is given by mouth, greater quantities would be necessary as much of the antianemic substance would probably be lost in the digestive process. When liver extract is given intravenously it is given in a form which is ready to be used immediately by the bone marrow, hence the early response.

Up to the present time it has been impossible to make an effective intravenous preparation from ventriculin. From the results obtained it is believed that the active principle, although generated in the stomach, does not exist in a free state in the dried stomach tissue as in the liver, but rather is bound up in some form which, when freed from protein, loses its potency or is present in the form of a precursor.[9]

The marked difference between the effect of a small amount of liver extract intravenously and the same amount by mouth probably lies in the rate of absorption. The liver extract when given orally is either absorbed with difficulty, partially destroyed, or the activity is delayed until the concentration in the tissues reaches a certain optimum. This accounts for the extremely rapid increase in red blood cells and hemoglobin with intravenous therapy, which is not seen with oral administration.

It would appear that intravenous liver therapy would be the most economical form of treatment in pernicious anemia. In the beginning it was hoped that intravenous therapy might be a suitable substitute for transfusion in an emergency. The one objection to this unrefined liver extract is the severe body reaction. It is unjustifiable to increase a patient's discomfort and to aggravate his already poor condition. If the reaction were slight or entirely eliminated by using a purified preparation, it could be used as a satisfactory therapeutic measure. More recently a refined liver extract has been prepared at the Simpson Memorial Institute which has a high degree of potency and does not produce untoward effects. The results following the use of this preparation will be reported in a later article.

Conclusions. 1. Two cases of pernicious anemia treated with liver extract intravenously are reported, in which a maximum reticulocyte response was produced in a shorter time than orally with a dosage which would have been wholly inadequate if taken by mouth.

2. The reticulocyte response began within 24 hours following liver extract therapy; the maximum was reached in 88 and 108 hours (Patients 1 and 2). The return to the pre-treatment level occurred in 264 hours (11 days).

3. The red blood cell count in Patient 1 increased 1,000,000 cells in 10 days, with a corresponding increase of 24 per cent hemoglobin. In the second patient there was also an increase of 1,000,000 cells in 10 days, with a hemoglobin increase of 28 per cent.

4. Lilly's Liver Extract (0.1 gm. per kg. body weight), when given intravenously, produces an effect lasting at least 2 weeks.

5. The liver extract used in these experiments is not suitable for clinical use because of the reactions.

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A CLINICAL METHOD OF MEASURING RED CELL DIAMETERS BY DIFFRACTION.*

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Hurst's[1] statement that "the most characteristic features of the blood in Addison's anemia are the anisocytosis and the increase in the average size of the red cells," has been substantiated by many workers using various methods of mensuration. Naturally there is some disagreement among the proponents of the several methods, particularly as to the necessity of measuring cells in plasma[2,3] or in a dried smear,[4] but from a purely practical viewpoint, a simple, rapid method of sufficient accuracy for clinical purposes is a desideratum.

The direct[5,6] method, using an ocular micrometer, gives the extremes and the mean from which a curve may be constructed.[7] However, it has disadvantages, not the least of which is that it is too tedious and time consuming for routine clinical use.

Another method is the measurement of photographically enlarged cells, which gives the same information as that obtained by the direct method. While somewhat less tedious it requires accurate magnification and good photography, and is also too time consuming for clinical use. The same objections apply to various modifications, such as projection on to a ruled screen, or use of the Euscope.[8]

The third method makes use of the hematocrit to obtain the total volume of cells in a given amount of blood, and dividing this volume by the number of cells per cubic millimeter will give the average cell volume. There are several modifications of this method,[9,10] but all require time for careful and repeated counts, and accurate observations of total volume, and even then there is the possibility of cumulative errors.

The fourth method uses the phenomenon of diffraction, first applied by Young (1773–1829) for the measuring of wool fibers. However, to Pijper[11,12,13] belongs the credit for the first practical application of this method to obtain red cell diameters. The principle consists in passing a beam of parallel rays of white light through a thin blood smear, and as the rays strike the periphery of each cell they are bent in toward the cell and also split into the component colors, so as to form concentric rings of the primary colors of the spectrum, ranging from violet in the center to red of the outermost circle in each series. These rings are repeated in sequence in the second series and so on.

The angle formed by the diffraction of the light rays is dependent

* Publication approved by the Surgeon-General, U. S. A.

upon the wave length of the color chosen, so that the size of the spectrum formed is in definite relation to the size of the cells and the distance of the screen upon which the spectrum is caught. Since the rays are bent inward, the size of the spectrum is in inverse proportion to the size of the cells.

Without going into details, the system of Pijper requires a suitable series of lenses to produce parallel(?) rays of light, an evenly made smear of cells, a collecting lens and finally a screen. The diameter of the ring of the color chosen is then measured and the calculation made from the following formula: $D = \frac{L\sqrt{F^2 + R^2}}{R}$ where D = diameter of the cells, L = wave length of the color used, F = the focal distance of the lens, and R = the radius of the spectrum.

Objections may be raised concerning the measurement of diameters, the effect of drying,[14] and so on, nevertheless granting all these objections, the fact remains that there is a decided difference between the spectrum produced by large, and that produced by small cells, a fact which may be verified by control measurements with the ocular micrometer, or other methods.

The use of Pijper's application is simple and inexpensive, but requires suitable space and a dark room. Moreover, the measurement of the circles with dividers is subject to error because the dividing line between colors is not clean cut. The writer knows of two ingenious modifications of Pijper's method, one by Emmons[15] and one by Eve,[16] the latter being in use in this laboratory.

The instrument about to be described is still another modification of the same principle for which only simplicity is claimed. There are no batteries, parallelizing lenses nor lamps costly or difficult to obtain.

This instrument occupies the upper end of the tube of a monocular microscope, the ocular having been removed. One objective is removed, as is the condenser and in place of the latter a light is inserted. On each side of the stage of the instrument is a millimeter scale with vernier, registering the position of a sliding shutter controlled by a thumbscrew (Fig. 1).

A properly made smear is placed, smear side down, on the stage and viewed through the pinhole ocular and the shutters set as nearly as possible at the extreme periphery of the red circle of the first series. The readings on each side are added, the result being the diameter of the spectrum. A table gives the corresponding approximate average cell diameter in microns; the whole procedure requiring about 30 seconds. This instrument has been used on hundreds of slides and has proved to be rapid, easy to use and practically foolproof. A smear of each case showing erythropenia is first observed with this instrument, and if the spectrum is smaller than normal, other methods are used to confirm the findings. If the

spectrum is smaller than normal it is advisable to examine the smear with the high dry to rule out rouleaux formation, for the cells must be evenly distributed on one plane. If too close together, superimposed or widely separated the result will not be satisfactory. A properly made smear produces a spectrum which at its center shows a small bright area of light occupying the position of violet, then a surrounding zone of pale yellow merging into yellow, orange and red, then the second series beginning with blue (Fig. 2).

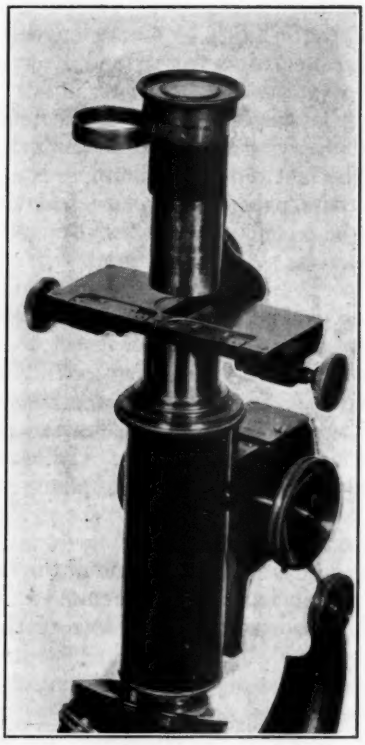

FIG. 1.—Showing mounting of instrument; the shutters, and thumbscrews which control them, and the vernier scales.

If a marked poikilocytosis is present, then even in a properly made smear the spectrum will appear diffuse and without the clean cut colors of the normal spectrum, due to the unequal and distorted diffraction, nevertheless the spectrum may often be measured with a satisfactory degree of accuracy (Fig. 3).

While textbooks of physics have been freely consulted and the opinions of physicists obtained, the writer is particularly indebted to Mr. Harry G. Ott for his interest and assistance in solving the

physics and mathematics involved. The conclusions reached are as follows: In this instrument the light from a pinhole at a standard distance falls on the smear. This light is, in a sense, bent by diffraction around each of the corpuscles of the smear, at a definite angle

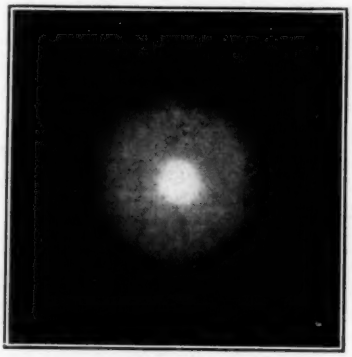

FIG. 2.—Halo of normal cells.

for each wave length and corpuscle size. This bending changes the direction of some of the light, so that it will be sent through an observing pinhole above the smear. Each corpuscle of the aggregate contributes its own portion of light, all of these overlapping to form a nearly evenly illuminated halo. The size of the halo will be determined, at the smear, by the corpuscle farthest from the axis of the instrument that can send light through the observing

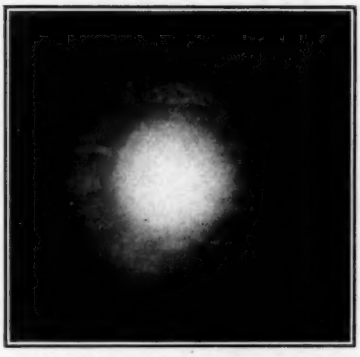

FIG. 3.—Halo of large cells, decidedly smaller and more diffuse, due to poikilocytosis.

pinhole. This is determined by the angle through which the light is bent by diffraction around the corpuscle. There is not an even distribution of light for all angles around the corpuscle. The intensity rises to maxima for certain angles, with minima of practically zero

intensity between. These minima serve to form a definite boundary to the halo formed by the maxima just preceding them. The first, and the brightest maximum formed by diffraction, lies at an angle between the two edges of the portion of the beam that is bounded by the corpuscle, and bent in such a direction as to pass through the observing pinhole. Let X = the pinhole source of

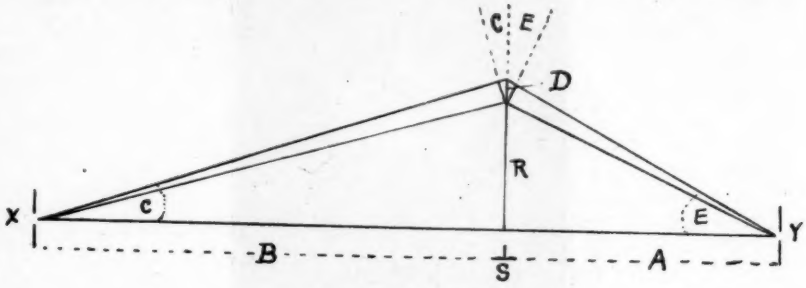

CHART I.

light, Y = the observing pinhole, D = diameter of corpuscle, R = radius of spectrum, L = wave length of light used, B = distance between illuminating pinhole and S, A = distance between observing pinhole and S, S = position of smear. The necessary difference in path of one wave length will be, D sin E + D sin C = L. But the angles are so small that the tangent and sine may be used interchangeably without significant error, hence the equation may be expressed:

$$D\,(\text{Tan } E + \text{Tan } C) = L$$

but $$\text{Tan } E = \frac{R}{A} \text{ and Tan } C = \frac{R}{B}$$

so $$DR\left[\frac{1}{A} + \frac{1}{B}\right] = L$$

or $$D = \frac{L}{R}\,\frac{AB}{A+B}$$

It can be seen from the above equation that for a certain size of corpuscle, the size of the halo varies directly as the wave length.

TABLE 1.—DIAMETERS OBTAINED BY PHOTOGRAPHIC AND BY MICRODIFFRACTOMETER METHODS.

No.	Photographic.	Microdiffractor.	Difference.
1	6.6 μ	6.6 μ	0.0 μ
2	8.0 μ	7.5 μ	0.5 μ
3	8.1 μ	7.7 μ	0.4 μ
4	8.0 μ	8.0 μ	0.0 μ
5	9.3 μ	8.7 μ	0.6 μ
6	9.2 μ	9.0 μ	0.2 μ
7	9.3 μ	9.3 μ	0.0 μ
8	9.3 μ	9.3 μ	0.0 μ
9	9.9 μ	9.8 μ	0.1 μ
10	10.4 μ	10.1 μ	0.3 μ

Acknowledgement is made of the coöperation of the Spencer Lens Company in meeting the mechanical difficulties.

Summary. A brief survey of various methods of red cell measurement is given.

A description and use of a simple micro-diffractometer using the phenomenon of diffraction for the measurement of erythrocyte diameters.

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THE EFFECT OF SPINAL DEFORMITIES ON THE HEART.

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Cardiac signs and symptoms resulting from deformities of the spine have been emphasized by Continental writers. However, the English and the American literature upon this subject is meager. Finley[1] has recently reported 4 cases of severe kyphoscoliosis, resulting in hypertrophy and dilatation of the heart with cardiac insufficiency and death. Reid[2] also reported a case of scoliosis causing cardiac hypertrophy and dilatation.

The material on which this study is based consists of 26 cases of spinal deformities, mostly of severe grade, involving the cervical or dorsal regions.* They were divided as follows: kyphoscoliosis, 15 (left, 1; right, 14); scoliosis, 5 (left, 2; right, 3); kyphosis, 4; lordosis, 2.

A history was taken and physical examination performed on all patients. The age, sex, spinal deformity and etiology are listed in

* Some of these patients were observed through the courtesy of Dr. A. M. Rechtman.

Table 1. One patient died of uremia; the remainder are alive, although some are incapacitated. The heart was studied fluoroscopically and orthodiagrams drawn in all but 3 cases; in the latter, 6-foot films were taken. Electrocardiograms were taken in 24 cases.

Scoliosis and Kyphoscoliosis. According to Vaquez,[3] Delpech, in 1848, was the first to record the association of spinal deformities with cardiac symptoms. However, Hippocrates,[8] in discussing gibbosities in his chapter on articulation, speaks of dyspnea as a common symptom "in those cases where the gibbosity is above the diaphragm." De Sauvages, Cullen and Bouvier, according to Boas,[4] have noted cardiac and respiratory disturbances in kyphoscoliosis, and in 1865 Sottas published a thesis on the effect of deviations of the vertebræ on the functions of respiration and circulation. Since that time the French and Germans have contributed many articles on the cardiac pathology and symptomatology of scoliosis and kyphoscoliosis, but the monograph of Bachmann[5] is the outstanding work on this subject.

TABLE 1.—CLASSIFICATION OF 26 CASES OF SPINAL DEFORMITIES.

	Age.						Sex.		Etiology.						
	1 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50.	Male.	Female.	Rickets.	Tuberculosis.	Poliomyelitis.	Muscular atrophy.	Empyema.	Dislocation of hip.	Unknown.
Kyphosis	..	1	..	..	2	1	0	4	..	4					
Scoliosis .	1	1	2	1	..	..	1	4	1	..	..	..	1	..	3
Kyphoscoliosis .	3	5	2	2	2	1	9	6	6	1	2	..	..	1	5
Lordosis .	..	1	1	..	..	..	1	1	..	..	..	1	..	..	1
Total .	4	8	5	3	4	2	11	15	7	5	2	1	1	1	9

Bachmann studied autopsy findings in 197 cases of his own and 79 cases collected from the literature. Cardiac abnormalities were found in 154 of 197 cases and, of these, 87 (56 per cent) had hypertrophy or dilatation of the right heart; in 27 (17.5 per cent) the left side was affected; in 40 (25.9 per cent) both sides. Displacement of the heart and kinking of the great vessels were noted in some cases. Similar findings have been reported by Romberg,[6] Rieder[7] and others. Death was due to heart failure in 116 (59.4 per cent) of 195 cases, but in 72 of these it was secondary to a pulmonary disorder.

Pathologic Physiology. Changes in the size and shape of the thorax and the consequent effect upon the lungs are doubtless the most important causes of the hypertrophy and dilatation of the right side of the heart noted in many of these cases. The lung on the side of the deformity is usually compressed, and, while it is merely atelectatic in many cases, Bachmann described it as a "tongue of fibrous tissue" in some of the marked cases. A compensatory emphysema on the opposite side further embarrasses the right heart. Since this deformity often begins in early life and is complete before bodily growth, the thorax lags somewhat behind and, as a result, the lung volume is diminished. Hippocrates[8] noted this and believed it the cause of dyspnea. According to Finley, the capacity of the lungs has been found to be reduced 20 to 60 per cent. Furthermore, the chest wall is limited in movement, and in many cases the diaphragm alone moves in respiration, and frequently this muscle is distorted. Thus the respiratory pumping effect is limited, or entirely lost in kyphoscoliosis. Rieder[7] believed that a faulty gaseous interchange occurs because of the various changes in the lungs. These factors may be presumed to burden the right heart. Aortic anomalies, such as alterations in its courses, twisting or kinking may burden the left heart.

Clinical Aspect. Scoliosis and kyphoscoliosis affecting the cervical and thoracic vertebræ are the most serious of the spinal deformities from the cardiovascular point of view. Mild cases produce very little change with the thorax, but in moderate and severe cases the changes are more marked. Some are relatively free of symptoms, and even with a severe deformity (Fig. 1) they may go on for many years, although dyspnea on exertion may be present. Most of the patients, however, present symptoms such as dyspnea, cyanosis and edema of the legs. These symptoms tend to progress in severity and a clinical picture suggesting right-sided heart failure often appears.[1]

Although bronchitis and pneumonia are frequent complications, there was evidence of tuberculosis of the lungs in only 1 of our 26 cases; another has had one tuberculous kidney removed and since then has developed tuberculosis in the remaining kidney. However, the distortion of the thorax is so great that examination of the lungs is exceedingly difficult and perhaps misleading; the possibility, therefore, exists that some of the other cases might have tuberculosis of the lungs. There is considerable difference of opinion with respect to the frequency of tuberculosis in association with these chest deformities.[5,10,11,12]

Interpretation of the physical findings is difficult. Expansion of the thorax is poor; in many cases the thorax is fixed. The lung on the side of the convexity may be atelectatic, and on the opposite side emphysematous; frequently both appear to be present in the same lung. The apex beat is often displaced. Percussion of car-

diac outlines is shown by orthodiagraphy frequently to be unreliable in severe cases of kyphoscoliosis. Apical systolic murmurs

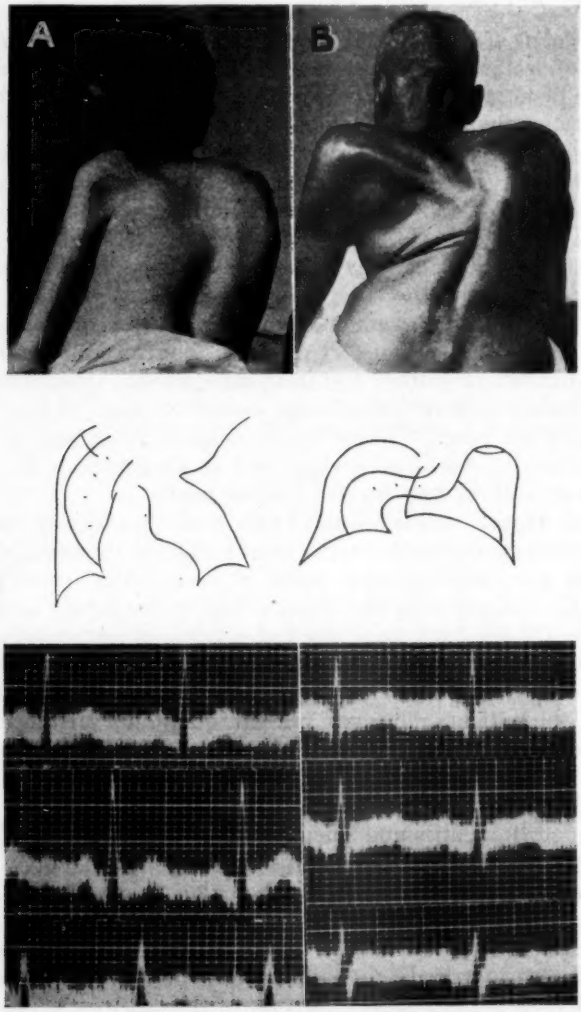

FIG. 1.—Two cases of severe right kyphoscoliosis in (*A*) a man, aged 35 years, and (*B*) a man, aged 61 years. Dyspnea on exertion was the outstanding symptom in both cases. Note the marked differences in shape and position of the heart. Orthodiagrams are anteroposterior views. The electrocardiograms show a normal electrical axis.

and accentuated pulmonic second sounds, especially in the severe cases, are common. Occasionally there is a rough systolic basal murmur, due possibly to a twist or kink of the aorta. Fig. 2 is

the orthodiagram of a case in which this possibility presented itself, for fluoroscopically the aorta seemed to make a sharp turn at the knob as it coursed downward and to the right to reach the spine. Substernal or precordial pain is an outstanding symptom in some cases.

Blood pressure variation between the two arms of more than 10 mm. of mercury occurred in 5 of the 15 cases of kyphoscoliosis. The greatest variation observed was 146 systolic and 86 diastolic in the right arm, and 104 systolic and 60 diastolic in the left. All cases, in which a difference of pressure was observed, had right kyphoscoliosis. In 3 cases the higher pressure was observed on the right side and in the other 3 cases on the left. Kinking or twisting of the aorta and its large branches may be concerned in this production of pressure differences, although they were absent in some of the severest cases.

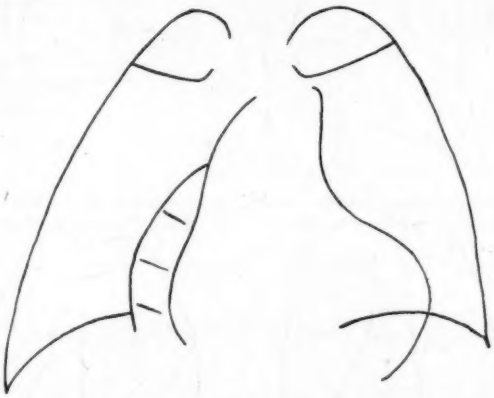

FIG. 2.—Orthodiagram of a woman, aged 38 years. Substernal pain was the chief complaint. Fluoroscopically the aorta appeared to make a sharp turn at the knob.

Cardiac rhythm was regular in all cases. Sottas reported cases of arrhythmia and Boas recently observed paroxysmal fibrillation in a young woman with scoliosis.

According to the literature, the vital capacity may be reduced as much as 65 per cent in severe cases, but in mild and moderate cases may be within normal limits. Flagstad and Kollman[12] found little reduction in cases involving the lower dorsal and lumbar regions.

Fluoroscopic Aspect. *Scoliosis.* The degree, level and direction of the curvature are important. High or middorsal scoliosis influences the heart more than lower dorsal deformity. Right scoliosis is by far the most common and is often complicated by some degree of kyphosis. The heart is displaced to the left; in some cases this is marked. In many cases of mild and moderate scoliosis the heart appears mitralized, the aortic knob small and, at times, the region

of the pulmonary artery prominent (Fig. 3, *A*). Brugsch[13] noted this configuration in 80 per cent of his cases and believed it to be due to aplasia. Frequently, however, this configuration is not seen.

The "mitralization" appears to depend on two factors: (1) Enlargement of the right ventricle; (2) rotation of the heart as the result of the spinal deformity. Enlargement of the right ventricle occurs in the majority of cases and causes the heart to be rotated

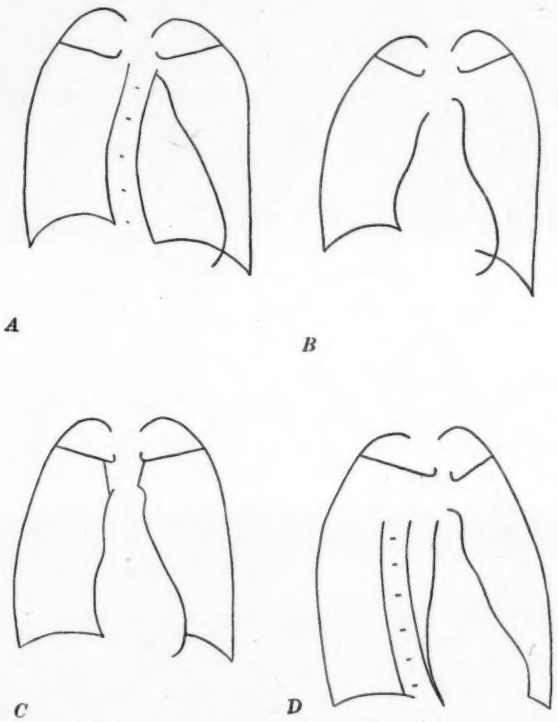

FIG. 3.—*A*, right scoliosis in a young man, aged 26 years; anteroposterior views; *B*, same patient in left anterior oblique 45 degrees; *C*, anteroposterior view of a normal young man, aged 26 years; *D*, after rotation to right anterior oblique 45 degrees. Note similarity of left borders in *A* and *D*.

upward, backward and to the left.[14] This rotation is apparently partially responsible for the configuration of the left border both in mitral stenosis and scoliosis.

Direct rotation around the longitudinal axis may also be important, as is shown by rotating a patient with right scoliosis to the left until the spine appears straight. The heart shadow then resembles the normal anteroposterior shadow. Conversely, by rotating a normal person to the right until the spine appears curved,

the heart shadow frequently resembles that seen in the antero-posterior position in right scoliosis (Fig. 3, *A–D*).

Sometimes the aortic knob appears very sharp and prominent, probably due to the sharp bend taken by the aorta as it courses to the right to reach the spine, and to its better visualization since it is not obscured by the spine.[17]

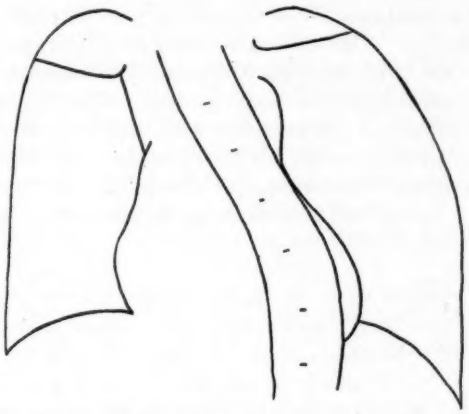

FIG. 4.—Left scoliosis in a boy, aged 7 years. Note the unusually wide aortic area and the central position of the heart. The shadow of the spine is within that of the heart.

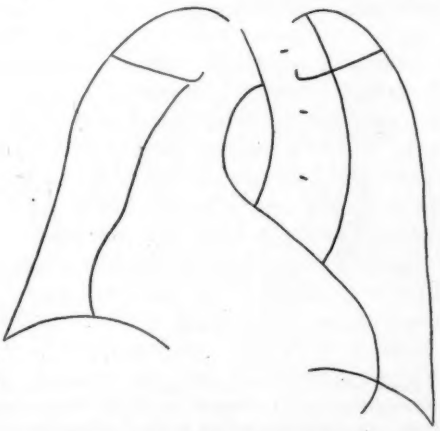

FIG. 5.—Left scoliosis, complicated by severe hypertension, in a man, aged 48 years. Note the "uncoiled" aorta and the clear space between the ascending aorta and spine. Descending aorta was not visualized.

In left scoliosis the heart assumes a more median position than normal and occasionally has the so-called aortic configuration. If the deformity is high, the aortic shadow appears considerably enlarged, for the aorta, in following the spine to the left, "uncoils"

itself (Figs. 4 and 5). Sometimes the descending aorta is seen projected alongside the ascending portion of the aorta. The aortic diameter, however, is not found widened. Low thoracic deformity will not cause a change in the aortic arch but the heart remains in the median position.

Kyphoscoliosis. Most cases of scoliosis are complicated by some degree of kyphosis. The configuration of the heart in these cases is usually not a combination of the effects seen in pure scoliosis and pure kyphosis, but is of a bizarre form and varies considerably from case to case (Fig. 1). Its form may be influenced by several factors, all of which are variable in their effect upon the heart. Among these are: (1) Spinal deformity and its consequent effect upon the bony thoracic cage; (2) hypertrophy and dilatation of the various chambers of the heart; (3) the height of the diaphragm; (4) coincident complications, such as hypertension and valvular disease.

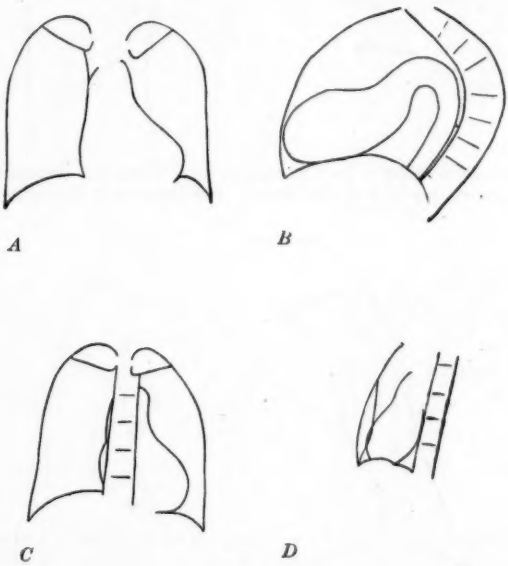

FIG. 6.—*A*, anteroposterior, and *B*, lateral views of a woman, aged 56 years, with kyphosis; *C*, anteroposterior, and *D*, lateral views of a boy, aged 9 years, with moderate funnel chest. All views have been reduced proportionately.

In severe cases the distortion of the thoracic cage is so great that the heart appears to assume a shape suitable to the space containing it, especially if the deformity occurs early in life when the organs have the greatest power of adaptability. This is exemplified by the contrast in shape of the heart in funnel chest and kyphosis; in the former the heart appears large but flat; in the latter, small

and long (Fig. 6, *A–D*). In kyphoscoliosis decrease of the anteroposterior diameter on one side and increase on the other side of the chest may be seen in the same patient, and its effect upon the heart will vary in different cases.

The deformity of the thorax also has a marked effect upon the diaphragm. In kyphoscoliosis the diaphragm is usually high and the effect further complicates the picture of a displaced and rotated heart of unusual shape.

Hypertrophy and dilatation of the various chambers of the heart will, of course, alter the cardiac silhouette. Factors concerned in the production of mitralization, such as right-sided enlargement and rotation, have been discussed above. Left-sided enlargement whether due to the deformity or to some coincident factor, such as hypertension, may also affect the cardiac silhouette (Fig. 5).

The position of the heart also varies from case to case. It is usually displaced to the left but in some cases it assumes a median position.

The transverse and descending aorta were visible in a few cases of right kyphoscoliosis. In each instance it crossed diagonally from its left position to reach the spine far to the right. In 2 cases observed postmortem, of which 1 is included in this series, the portion of the aorta which would normally be the descending aorta coursed directly to the right to reach the spine, and then closely followed its curve downward. Klawansky[9] and Dwight[18] have described cases in which a remarkable deformity of the aorta resulted from following a tortuous spine.

Electrocardiographic Aspect. Electrocardiograms were taken of 4 cases of scoliosis and 14 cases of kyphoscoliosis. Except for axis deviation the tracings were normal in 16 instances. The 2 abnormal electrocardiograms were from patients with kyphoscoliosis. In 1 the *Q–R–S* complex in Lead II was definitely split; in the other there was evidence of marked myocardial disease. The latter electrocardiogram, however, was from a patient with marked hypertension (190 systolic and 158 diastolic) and also a pituitary disorder. In no instance was there any disturbance in conduction, although Vaquez has noted defects in conduction in some of his cases.

Three cases of kyphoscoliosis and 2 of scoliosis showed a left axis deviation. One of the former, however, occurred in the case of hypertension mentioned above. One case of kyphoscoliosis showed a right axis deviation. The most marked cases, however (Fig. 1), showed a normal axis. Two possible explanations are offered for the infrequency of axis deviation, despite marked displacement of the heart.

1. In a small minority of cases the heart may be displaced as a whole without rotation on its anteroposterior or longitudinal axis.

2. Rotation of the heart around its longitudinal axis compensates for the rotation around the anteroposterior axis. According to

Meek and Wilson,[15] displacement of the heart to the right or left usually causes a combined rotation on both axes and produces electrocardiographic changes which cannot be predicted, because of the opposing effects of simultaneous rotation around the anteroposterior and longitudinal axis.

Kyphosis. Pure kyphosis is relatively uncommon. According to the literature most of the patients do not present cardiac complaints. The increase in the anteroposterior diameter of the chest compensates for the decreased transverse and vertical diameters. The lung capacity is not reduced and there is little effect upon the circulatory system, although the shape and position of the heart and great vessels are considerably altered. Three of the 4 cases of kyphosis in this study presented cardiac symptoms, but in each case a complicating factor (hyperthyroidism in 2, arteriosclerosis and hypertension in 1) was probably responsible.

On fluoroscopic examination in the anteroposterior view, the heart appears small or normal in size, centrally placed and dense. In the lateral view it appears large. Thus its shape is altered, the anteroposterior diameter at times being greater than the transverse (Fig. 6, *A–B*). The arch of the aorta seems less rounded—in fact, almost flattened—as it extends posteriorly to follow the spine. The barium-filled esophagus which appears short in the anteroposterior view is seen to take a normal course.

Electrocardiograms were normal except for the fact that in 1 patient with hyperthyroidism auricular fibrillation was present.

Lordosis. Mild grades of lordosis are common, but have no effect upon the heart and are, therefore, not included in this study. Severe grades, affecting the thoracic spine, are uncommon unless complicated by some degree of scoliosis. According to Barie,[16] many patients with lordosis do not present cardiovascular symptoms, although some complain of dyspnea on exertion. The 2 cases included in the present study had no cardiac symptoms. Both were, however, incapacitated from other causes.

According to Barie the heart is displaced to the left, but in our 2 cases no displacement was noted. The anteroposterior diameter of the heart in both cases was reduced, in 1 markedly (Fig. 7).

The electrocardiogram in 1 case (infectious arthritis) showed inverted *T* waves in Leads I and II. In the other, it was normal except for a left axis deviation.

Summary and Conclusions. 1. Spinal deformities, especially scoliosis, and kyphoscoliosis have a profound effect upon the lungs, and the effect upon the heart is probably secondary to the latter in most cases. Kinking or twisting of the great vessels as the result of displacement of the heart may be responsible for certain cardiac signs and symptoms.

2. Most patients with kyphoscoliosis and severe grades of scoliosis have signs of right-sided disturbance of cardiac function. How-

ever, they may live for years, many being restricted in activity because of dyspnea on exertion. Some are cyanotic and a few show edema of the legs. According to the literature most cases die of a pulmonary complication.

3. Kyphoscoliosis causes marked changes in the size, shape and position of the heart. The shape and position of the heart vary considerably from case to case.

4. The aorta tends to follow the spine in spite of the deformity. In 2 cases of right kyphoscoliosis observed postmortem the aorta coursed directly across the thorax to reach the spine.

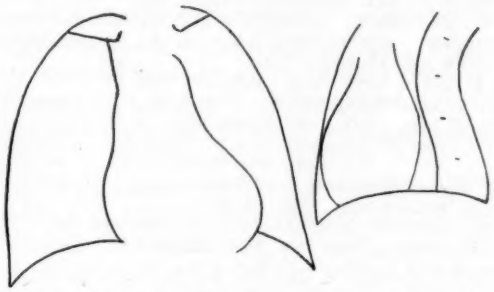

FIG. 7.—Anteroposterior and lateral views of a young boy, aged 10 years, with lordosis. Note the comparatively small anteroposterior diameter.

5. Pure scoliosis due to organic disease is relatively uncommon and is usually right-sided. In the latter the heart is displaced and often rotated to the left, causing it to appear "mitralized." The aortic knob appears very sharp in some cases. Left scoliosis causes the heart to become centrally placed and the aortic area to appear widened. The aortic diameter, however, is not increased.

6. Three of the 4 cases of kyphosis included in this study presented cardiac complaints, but there were complicating factors in each case sufficient to account for the symptoms. In pure kyphosis the anteroposterior transverse diameter ratio tends to be greater than normal.

7. Two cases of lordosis presented no cardiac symptoms. The anteroposterior-transverse diameter ratio was smaller than normal in both.

8. Except for axis deviation in six instances, the electrocardiogram was normal in 20 of 24 cases of spinal deformity. Two of the 4 abnormal electrocardiograms were in patients with hyperthyroidism and hypertension. The infrequency of axis deviation despite displacement and rotation of the heart is probably due to the opposing effects of rotation around longitudinal and anteroposterior axes.

NOTE.—This study was undertaken at the suggestion of Dr. Stengel. Dr. Wolferth has made many valuable suggestions.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

I. The Frequency and the Degree of Response to Carotid Sinus Pressure Under Various Diseased States.

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It has been known for many years that pressure on the carotid artery at the level of the cricoid cartilage would produce slowing of the heart. Perry[1] observed this phenomenon as long ago as 1779 in a case of hemiplegia. In 1868 Czermak[2] called attention to this reaction and quoted Pflüger, who first obtained this effect on vagal stimulation in animals. In the same year Sustschinsky[3] showed that this vagal response in animals could be obtained in one of three ways: (1) by removal of the accelerator nerves; (2) by lessening the coronary blood supply to the heart; (3) by decreasing the ventilation of the blood.

Until recent years, the mechanism of the production of this reaction was considered to be a direct mechanical stimulation of the vagus nerve running in the carotid sheath. It was found, however, that in certain individuals, a minimum amount of pressure, insufficient to affect the vagus, produced results. Besides, Scherf[4] suc-

ceeded in producing slowing of the heart by stimulation of the central end of the cut vagus in an individual who underwent a vagotomy operation for therapeutic purposes. It was, therefore, evident that it was a reflex rather than a direct vagal reaction which was responsible for the phenomenon.

The mechanism of this reflex remained to be worked out by Hering[6] in a series of animal experiments. He showed that this reflex originates in the wall of the sinus of the internal carotid artery near its junction with the external carotid. The afferent fibers run in the glossopharyngeal nerve where they enter by a branch, termed by him the "Sinus Nerve" which starts in the sinus wall. Mechanical irritation of the sinus wall, either external or internal, results in two independent reflexes—one producing slowing of the heart and another a fall in blood pressure. The efferent impulse which slows the heart is carried by the vagus. Hering further showed that the sinus nerve has constant tonicity, for its severence results in a slight, permanent rise in blood pressure and pulse rate.

Although reflex slowing of the heart occurs in all experimental animals as well as in man by clamping the carotid sinus, ordinary mechanical stimulation caused by pressure upon the sinus area from without produces slowing only in a limited number of cases. It has been found to accompany various diseased states. Perry,[1] as said before, observed it in a case of hemiplegia. Czermak,[2] Quincke[6] and De la Harpe[7] found it in connection with cerebral disease. Concoto[8] observed it in a case of epilepsy and arteriosclerosis and in another case of cardiac hypertrophy and endocarditis. De Cerenville[9] observed it mainly in cerebral disease, less constantly in general arteriosclerosis, occasionally in convalescence from acute disease, but almost never in health. Wenckebach[10] found marked response to very slight pressure to occur in very badly diseased hearts. Hering[6] obtained active response in localized sclerosis of the carotid artery, especially at the sinus of the internal carotid, and quoted Koch who found localized sclerosis of the carotid sinus in 4 autopsy cases who presented a marked reaction during life. Danielopolu and Missirlin[11] considered an exaggerated reaction to pressure a valuable diagnostic means in chronic myocardial disease existing in a latent form. Braun and Samet[12] presented a series of cases with coronary disease that showed marked response. They also produced coronary lesions in animals and found that such lesions increased vagal response. Their conclusions were that heightened response to vagal stimulation is indicative of coronary disease and is of grave prognostic significance. Most of their patients who showed an exaggerated response died in a few weeks or months. Sanders[13] found some response in normal persons.

It would seem, then, that this reflex vagal response accompanies certain pathologic conditions and may even occur in apparently normal individuals. Its importance as a diagnostic means in cardiac

disease, stressed particularly by Concoto,[8] Wenckebach,[10] Danielopolu and Missirlin,[11] and Braun and Samet[12] makes it of special interest. The test is a simple one and, if it has any value in diagnosis, it certainly deserves careful consideration and more widespread use.

With a view of determining the frequency of occurrence of this reflex in various diseased states and in an attempt to ascertain its diagnostic significance, I performed the test on a series of 345 cases obtained from the cardiac clinic and the ward service of the Harbor Hospital, the cardiac clinic of the New York Post-Graduate Hospital, the general medical ward service of the Coney Island Hospital, and from private practice. The cases were divided into the following five groups according to the main diagnosis: *Group I*, coronary artery disease with definite myocardial damage; *Group II*, hypertension and hypertensive heart disease; *Group* III, rheumatic heart disease; *Group IV*, patients with abnormal signs or symptoms referable to the heart, but showing no definite evidence of heart disease; *Group V*, general constitutional disease (non-cardiac). This paper is a preliminary report, dealing with the male and female response to carotid sinus pressure in the various groups, and the degree of such response in each group.

Detailed Analysis of Cases. GROUP I (115 cases). The predominant diagnosis was coronary sclerosis with definite evidence of more or less myocardial disease. Most of these cases showed evidence of general arteriosclerosis; 41 presented the anginal syndrome; 16 had attacks of coronary occlusion; 28 had no angina, but presented other evidence of coronary disease. In addition to coronary changes, 7 cases had chronic bronchitis, 2 diabetes, 1 bronchial asthma, 2 obesity, 8 were in the period of menopause, and 5 showed evidence of congestive heart failure.

GROUP II (56 cases). The predominant diagnosis was hypertension. Four cases showed evidence of aortic sclerosis with dilatation; 7 had coronary occlusion; 5 were in the menopause; 24 had considerable cardiac enlargement; 1 had mitral stenosis, probably of rheumatic origin; 1 had chronic nephritis; 2 cerebral sclerosis; 6 diabetes; 1 a diffuse aneurysm of the aorta; 1 had congestive heart failure; 4 had no complications or associated disease.

GROUP III (50 cases). This group comprised a variety of chronic rheumatic cardiovalvular disease. Only 5 cases had acute rheumatic cardiac involvement. Of the chronic cases there were 21 with mitral insufficiency and stenosis, 1 with mitral stenosis and aortic insufficiency, 10 with mitral stenosis, 6 with mitral insufficiency, 2 with aortic insufficiency, 1 with double mitral and aortic insufficiency, 1 with aortic stenosis, 1 with double mitral and aortic stenosis, and 1 with mitral and aortic insufficiency. Three cases were fibrillating, 5 cases showed evidence of congestive failure, 1 case of mitral stenosis showed first degree heart block.

GROUP IV. Predominantly neurocirculatory asthenia (58 cases). They showed some symptoms or signs referable to cardiovascular disturbances but no definite evidence of anatomic cardiac pathology and no definite etiology pointing to heart diseases. Twenty patients complained of precordial pain; 15 complained of asthenia, occasional palpitation and some shortness of breath on exertion; 2 had angioneurotic edema; 12 showed simple tachycardia, marked nervous irritability and vasomotor disturbances; 2 cases presented moderate thyrotoxicosis; 3 were diabetics; 4 presented disturbances incident to the menopause.

GROUP V. No cardiovascular disturbances (66 patients). Sixteen patients suffered from various forms of neurasthenia; 4 had marked obesity; 5 had chronic pulmonary tuberculosis, 2 of whom showed evidence of activity; 1 had Addison's disease; 2 had mild thyrotoxicosis; 4 suffered from gastro-duodenal ulcers, 6 from chronic cholecystitis; 1 from sacro-iliac arthritis; 1 had a pituitary tumor; 3 had chronic appendicitis; 1 chronic nephritis; 1 gastric carcinoma; 1 pyelonephritis; 1 cerebrospinal lues; 2 chronic bronchitis and bronchiectasis; 1 osteoarthritis of the knee joints; 2 bronchial asthma, and 1 was in convalescence from lobar pneumonia; 5 had no definite disease but complained of chronic constipation. Two of these had evidence of chronic foci of infection in the tonsils and sinuses.

Individual Group Response to Carotid Pressure. Table 1 represents the responses of males and females in the various groups to carotid sinus pressure. In each group we have the number of males and females examined—the total number responding with the percentage response, the number responding to both-sided pressure, the number responding to left-sided pressure only, and the number responding only to right-sided pressure. In a separate column is the average for all groups showing the above responses. Fig. 1 is a graphic representation of the percentage response in the various groups as well as in the average for all groups.

It will be noted that the total number of patients responding is greatest in Groups I and II, less in Groups III and V, and least in Group IV. In all groups except in Group I, the total number responding among females is definitely smaller than among males.

The number of patients showing complete response, that is the response to both right- and left-sided pressure, is greatest in Groups I, II and III. In Groups IV and V the number showing complete response is greatly diminished. That is, in total response as in complete response, the females show a definitely smaller percentage response than males in each group as well as in the average for all groups.

In single-sided response, there is a greater percentage in Groups III, IV and V than in Groups I and II, and generally a greater percentage among females than among males. In all groups,

however, the number showing single-sided response is markedly smaller than those showing complete response, and the number responding on right-sided pressure is smaller than the number responding on left-sided pressure.

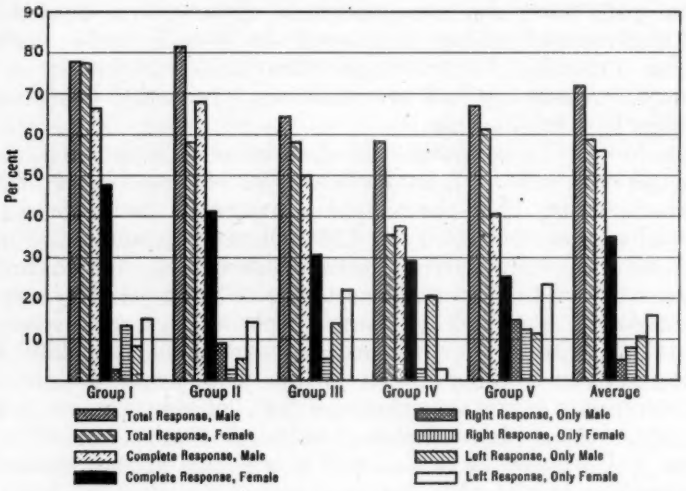

FIG. 1.—Percentage response to vagal stimulation. Total response includes all response. Complete response includes response to both, right and left stimulation in the same patient. Right response includes only response to right stimulation. Left response includes response only to left stimulation.

TABLE 1.—RESPONSE TO CAROTID SINUS PRESSURE AMONG MALES AND FEMALES.

Groups.	Total No. of cases.		Total not responding.		Total responding and percentage response.				Complete response and percentage.				Left response alone and percentage.				Right response alone and percentage.			
	Male.	Female.	Male.	Female.	Male.		Female.		Male.		Female.		Male.		Female.		Male.		Female.	
					No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	71	44	16	10	55	77.2	34	77.2	47	66.2	21	47.7	6	8.4	7	15.9	2	2.8	6	13.6
II	22	34	4	14	18	81.8	20	58.8	15	68.2	14	41.2	1	5.4	5	14.7	2	9.1	1	2.9
III	14	36	5	15	9	64.3	21	58.3	7	50.0	11	30.5	2	14.3	8	22.2	0	0.0	2	5.5
IV	24	34	10	22	14	58.3	12	35.2	9	37.5	10	29.4	5	20.8	1	2.9	0	0.0	1	2.9
V	27	39	9	15	18	66.6	24	61.5	11	40.7	10	25.6	3	11.1	9	23.1	4	14.8	5	12.8
Total	158	187	44	76	114	72.1	111	59.3	89	56.3	66	35.3	17	10.8	30	16.0	8	5.0	15	8.0

"Complete response" includes response to both right- and left-sided pressure.

To summarize, we find: (*a*) That the greatest number responding to carotid sinus pressure is in the arteriosclerotic and the hypertensive groups, although the other groups also responded in high percentages. The least response is shown in neurocirculatory

asthenia. (*b*) The response to both-sided pressure is greatest in arteriosclerotic, hypertensive and rheumatic heart disease, and much less in the non-cardiac groups where there seems to be a greater tendency toward response to one-sided pressure, especially left-sided. (*c*) Females show a much smaller incidence of response in all groups and one-sided response is more frequent in them than in males.

Degree of Slowing. The degree of slowing was determined by comparing the heart rate before and after sinus pressure was applied. The amount of pressure used was the maximum required in a given case to produce the maximum slowing. This amount varied with different patients. In many cases, very little pressure produced stoppage of the heart for as long as 2 to 7 seconds. In others, considerable pressure produced only 10 to 25 per cent slowing. In a few cases, instead of slowing, an acceleration of the heart was observed, probably due to pain or excitement incident to pressure, or perhaps to a cardio-accelerator reflex set up by the pressure.

In many cases the greatest amount of slowing occurred about 1 or 2 seconds after the maximum pressure was applied, and lasted as long as pressure was maintained. In all cases, except where the heart stopped, the rate obtained by pressure was multiplied by the time in seconds to arrive at the rate per minute. Thus, if the rate obtained was 4 beats in 6 seconds of pressure, the rate was considered to be 40 per minute. With a previous rate of 75 per minute, the slowing was taken to be about 53 per cent.

In some cases the slowing outlasted the pressure. This occurred in those cases which responded to a minimum amount of pressure. Here the pressure was at once discontinued for fear of untoward effects of heart stoppage, for in all these cases the heart stopped for 2 or more seconds. In most cases the heart rate would slow down on the first 5 or 6 seconds of pressure and would rise again on the continuation of such pressure.

The degree of slowing was divided into three grades—that of less than 25 per cent of the original rate, that of 25 to 75 per cent, and that with stoppage of the heart for more than 2 seconds. We shall consider these degrees of slowing as mild, moderate and marked, respectively.

Table 2 and Fig. 2 represent the various groups responding according to these degrees of slowing. It will be noticed that the percentage of patients showing mild degree of slowing is greatest in Groups IV and V and less in Groups, I, II and III. In all the groups the number of females responding in a mild degree invariably exceeds the number of males.

In all groups the predominant slowing is moderate in degree, and the number of females responding in that degree is also greater except in the non-cardiac groups where the number showing a marked degree of slowing is small, and the males respond predominantly in moderate degree.

In the cardiac groups, especially the arteriosclerotic and the rheumatic, there is a greater tendency toward a marked degree of slowing, and a greater number of males respond to such degree than females. In Group IV, the number showing a marked response is comparatively small. In Group V there seems to be a greater tendency for females to show such response. In the average for all groups, males show marked response in greater number than females.

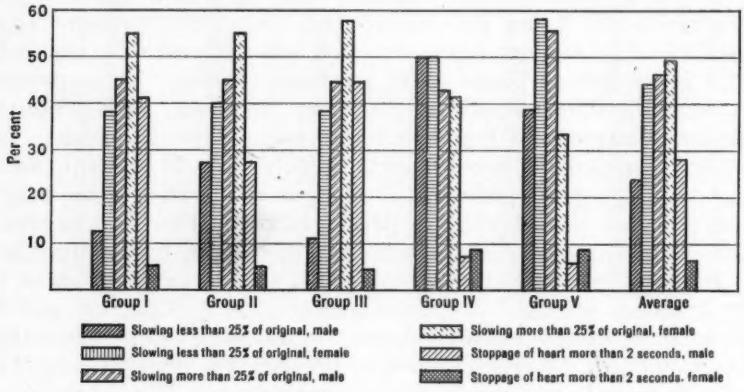

FIG. 2.—Degree of slowing.

TABLE 2.—DEGREE OF SLOWING IN THE VARIOUS GROUPS.

Groups.	Slowing. Less than 25% of original.				Slowing. More than 25% of original.				Heart stopped.			
	Male.		Female.		Male.		Female.		Male.		Female.	
	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.
I	7	12.7	13	38.2	25	45.4	19	55.8	23	41.8	2	5.8
II	5	27.7	8	40.0	8	44.4	11	55.0	5	27.7	1	5.0
III	1	11.0	8	38.1	4	44.4	12	57.1	4	44.4	1	4.7
IV	7	50.0	6	50.0	6	42.8	5	41.6	1	7.1	1	8.3
V	7	38.8	14	58.3	10	55.5	8	33.3	1	5.5	2	8.3
Total	27	23.6	49	44.5	53	46.5	55	49.5	34	28.0	7	6.3

The percentage of slowing was arrived at by comparing the rate before with the rate after carotid sinus pressure was applied. The percentage number of cases showing the various degrees of slowing was calculated on the basis of the number of cases responding.

To summarize, we find: (*a*) That there is a greater tendency toward a mild or moderate degree of slowing in the non-cardiac groups of patients and moderate or marked in the cardiac groups. (*b*) Females show a greater tendency than males toward mild response, and lesser tendency toward marked response.

Discussion. It will be seen from the observations presented in this paper that reflex slowing of the heart produced by carotid sinus pressure occurs in a variety of conditions. The greatest incidence of response, especially of marked response to comparatively little pressure, occurs in arteriosclerosis and hypertension with evidence of severe myocardial damage, as well as in rheumatic heart disease. Its occurrence in other conditions, even if in a milder degree, and its absence in some very severe forms of cardiac disease call for broader explanations of this phenomenon than the mere presence of cardiac disease. Besides, the diminished response, both in incidence and degree, in neurocirculatory asthenia and in females cannot be explained merely on the bases of local disease. We must infer the existence of a vagotonic predisposition inherent in certain individuals, making them susceptible to reflex vagal activity. Although the Eppinger and Hess theory[14] of vagotonic and sympatheticotonic constitutions is applicable to a very limited number of cases, we cannot doubt the existence of a vagotonic predisposition without in most cases showing symptoms under ordinary circumstances, but exhibiting itself under adverse circumstances and caused by external stimulation. Judging from our findings, such vagotonic tendency is much smaller in females than in males and is also small in neurocirculatory asthenia. The actual existence in females and in neurocirculatory asthenia of a greater tendency toward sympathetic nerve response is evidenced by the frequent occurrence here of simple tachycardia and changing temperament.

We cannot doubt that local disease such as sclerosis at the carotid sinus, in the brain or in the heart affecting the various components of the reflex vagal arc may lower the threshold of irritability of that arc, thereby increasing the response. This is evident from the reports of the authors quoted in the preliminary remarks in this paper. It seems, however, that an inherent tendency toward vagal response is necessary to get the effects of carotid sinus pressure, even in those cases where such effects are expected to be present.

Summary and Conclusions. Carotid sinus pressure was carried out on a series of 345 cases, consisting of 158 males and 187 females. The cases were divided into the following five groups: (1) Arteriosclerotic heart disease; (2) hypertension and hypertensive heart disease; (3) rheumatic heart disease; (4) neurocirculatory asthenia, and (5) general constitutional disease with no cardiac abnormalities. There was a greater number of patients showing slowing, and the degree of slowing was much more marked in arteriosclerotic and hypertensive groups. The rheumatic heart disease and the general constitutional disease groups were next in number and degree of slowing. The neurocirculatory asthenia group showed the least number and lowest degree of slowing. In all groups, females showed a definitely milder grade of slowing than males, and the number responding was definitely smaller.

A possible explanation for the variation in response is that a vagotonic predisposition is necessary for an effective response. This predisposition is greater in males, and less in neurocirculatory asthenia. Local disease, as sclerosis in the carotid sinus, vagal center or heart, greatly accentuates the reflex in the predisposed individual.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

II. THE RESPONSE TO CAROTID SINUS PRESSURE AT VARIOUS AGES AND HEART RATES AND RHYTHMS.

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This paper deals with a further analysis of the series of cases reported in the preceding paper (I) as to the frequency of response to carotid sinus pressure at various ages, and under various heart rates and rhythms. The object of this study is to determine if vagal response is altered by age, and if a heart already under increased vagal influence such as in sinus bradycardia and sinus arrhythmia is more susceptible to reflex vagal stimulation than a heart under predominant sympathetic control such as in simple tachycardia.

Frequency of Response at Various Ages. All patients in the various groups were divided according to their ages into the following four subgroups: adolescents (5 to 20 years of age); adults (21 to 40); middle age (41 to 60); and old age (61 to 80).

We find in Table 1 and Chart I that in the average for all groups

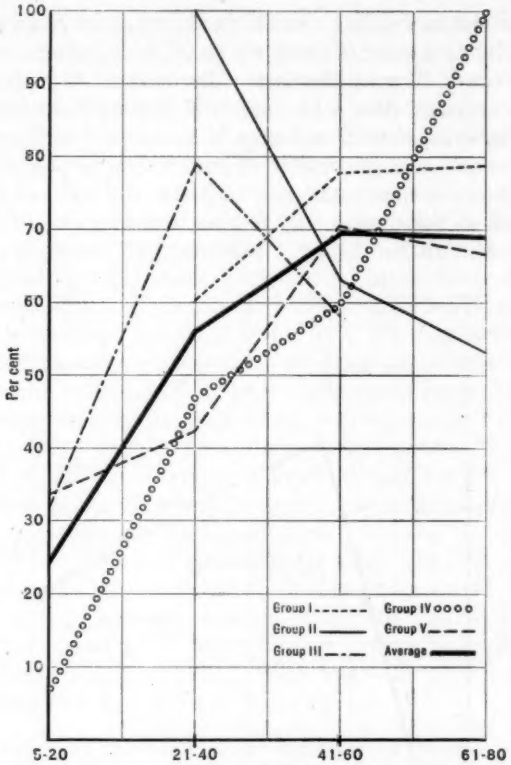

CHART I.—Percentage response to carotid sinus pressure at given ages. Ordinate represents percentage response. Abscissa represents age groups.

TABLE 1.—RESPONSES TO CAROTID SINUS PRESSURE, AT VARIOUS AGES AND IN THE VARIOUS GROUPS.

Groups.	Ages, 5 to 20 years.			Ages, 21 to 40 years.			Ages, 41 to 60 years.			Ages, 61 to 80 years.		
	No. responding.	No. not responding.	Per cent responding.	No. responding.	No. not responding.	Per cent responding.	No. responding.	No. not responding.	Per cent responding.	No. responding.	No. not responding.	Per cent responding.
I . .	0	0	0.0	6	4	60.0	56	16	77.7	25	8	78.8
II . .	0	0	0.0	3	0	100.0	24	14	63.2	8	7	53.3
III . .	6	13	31.6	15	4	78.9	7	5	58.3	0	0	0.0
IV . .	1	12	7.7	11	12	47.8	12	8	60.0	2	0	100.0
V . .	2	4	33.3	14	19	42.4	17	7	70.8	2	1	66.6
Total av.	9	29	23.9	49	39	55.7	116	50	69.9	37	16	69.0

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

as well as in the individual groups, the number of cases responding to carotid sinus pressure is small up to 20 years of age, and greatly increases between 21 and 40 years. The maximum response occurs between 41 and 60, after which age no definite further increase is noticed. The exceptions found may be accounted for by the insufficient number of cases observed. Thus, in the hypertensive group the curve shows a maximum rise between the ages of 21 and 40, but inasmuch as there were only 3 cases in that group at these ages, no conclusions can be drawn. Likewise, in the rheumatic heart

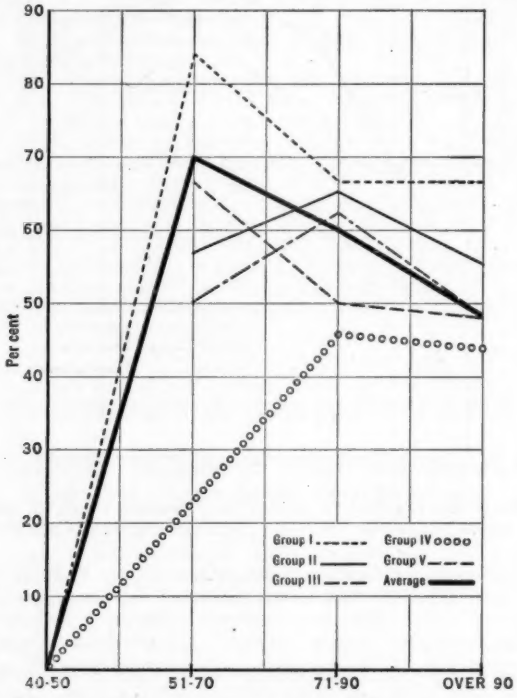

CHART II.—Percentage response to carotid sinus pressure with given heart rates. Ordinate represents percentage response. Abscissa represents rate of heart per minute.

disease group, the curve seems to show the highest peak between 21 and 40. Here there is a greater number of cases between those ages than at later ages, and again no definite conclusions can be drawn. In the neurocirculatory asthenia group, there seems to be a tendency toward a marked further rise after 61 years of age, but inasmuch as there are only 2 cases in this group above that age, no significance is to be attached to this rise.

In the arteriosclerotic and hypertensive groups, there were no cases younger than 20 years. In the rheumatic heart disease group,

there were no cases older than 60 years. The appropriate colums in those groups are therefore represented by zeros, and the respective curves start or end at ages where figures are available.

Frequency of Response With Various Heart Rates. In the determination of the frequency of response to carotid sinus pressure in individuals showing different heart rates, the various groups of patients were divided into the following four subgroups: (1) those showing very marked bradycardia (the rates being 40 to 50 beats per minute); (2) those with moderate bradycardia (rates varying between 51 and 70); (3) those with normal rates (between 71 to 90), and (4) those with tachycardia (rates of over 90 beats per minute).

It will be noticed (Table 2 and Chart II) that with heart rates of 50 or less beats per minute, no slowing was obtained by carotid sinus pressure. Although only 4 such cases have been observed and therefore no definite conclusions can be drawn, the absence of slowing in every case is nevertheless significant. With moderate bradycardias, on the other hand, the tendency for response appears to be maximum in the average, and in the arteriosclerotic and the various constitutional disease groups, while in the other groups it is slightly less than with normal heart rates. In view of the smaller number of cases in the moderate bradycardia group as compared with the group showing normal rates, the slightly diminished response here among the other disease groups is undoubtedly due to discrepancies in numbers. With rates of over 90, there is a decided drop in response in each group.

TABLE 2.—RESPONSE TO CAROTID SINUS PRESSURE AT VARIOUS HEART RATES IN THE VARIOUS DISEASE GROUPS.

Groups.	Rate, 40 to 50.			Rate, 51 to 70.			Rate, 71 to 90.			Rate, over 90.		
	No. responding.	No. not responding.	Per cent responding.	No. responding	No. not responding.	Per cent responding.	No. responding.	No. not responding.	Per cent responding.	No. responding.	No. not responding.	Per cent responding.
I . . .	0	2	0	25	5	83.3	36	17	67.0	20	10	66.6
II . . .	0	0	0	4	3	57.0	27	14	65.8	5	4	55.5
III . . .	0	0	0	3	3	50.0	17	10	62.9	8	9	47.2
IV . . .	0	2	0	1	3	25.0	12	14	46.2	11	14	44.0
V . . .	0	0	0	2	1	66.6	18	18	50.0	13	14	48.1
Total . .	0	4	0	35	15	70.0	110	73	60.1	57	51	48.3

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

Frequency of Response With Various Rhythms of the Heart. The entire series of cases presented three heart rhythms. Many cases in each rhythm showed premature contraction, but no separate

subdivision of such cases was made. There were 287 cases with regular sinus rhythm, 49 cases with definite sinus arrhythmia, and only 9 cases with auricular fibrillation. The preponderance in the number of cases of normal sinus rhythm over the other two rhythms, and especially over auricular fibrillation, makes comparison of response under the three rhythms not entirely reliable. Some deductions may, however, be made from the comparison.

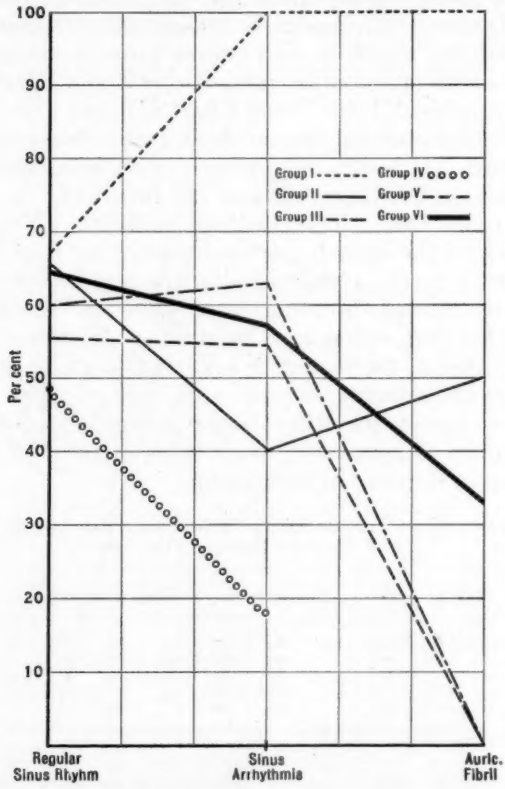

CHART III.—Percentage response to carotid sinus pressure in various rhythms. Ordinate represents percentage response. Abscissa represents rhythm.

We find (Table 3 and Chart III) that the curve of average response has its highest peak under regular sinus rhythm, a lower level under sinus arrhythmia, and lowest under auricular fibrillation. This applies with slight variation to all other curves except that of arteriosclerotic heart disease. Here there is a definitely greater proportional response with sinus arrhythmia and with auricular fibrillation. In both, all cases with arteriosclerotic heart disease responded. Although the number of such cases is small, complete response without

exception has some significance. In the hypertensive group, the curve has a tendency to rise in auricular fibrillation. As there were only 2 cases here, and only 1 responded, such rise has no significance. The lower response in sinus arrhythmia than in regular sinus rhythm in the average curve is undoubtedly due to the great discrepancy in a number of cases in the two rhythm groups.

TABLE 3.—RESPONSE TO CAROTID PRESSURE WITH VARIOUS RHYTHMS OF THE HEART IN THE VARIOUS DISEASE GROUPS.

Groups.	Regular sinus rhythm.			Sinus arrhythmia.			Auricular fibrillation.		
	No. responding.	No. not responding.	Percentage response.	No. responding.	No. not responding.	Percentage response.	No. responding.	No. not responding.	Percentage response.
I	68	34	66.6	11	0	100.0	2	0	100.0
II	32	17	65.3	2	3	40.0	1	1	50.0
III	21	14	60.0	7	4	63.6	0	4	0.0
IV	23	24	48.9	2	9	18.1	0	0	0.0
V	30	24	55.5	6	5	54.5	0	1	0.0
Total	174	113	64.1	28	21	57.1	3	6	33.3

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease.

Discussion. The essential findings recorded in this paper are: (1) That the carotid sinus reflex occurs infrequently in adolescence, increases in adult life, and reaches a fastigium in middle life. (2) That in marked bradycardia, no further reflex vagal slowing is obtained, and in tachycardia, the response is greatly diminished. The highest response occurs in the moderate bradycardia. (3) In sinus arrhythmia there is no appreciable difference in response over normal sinus rhythm except in arteriosclerotic heart disease where there is increased vagal response with this arrhythmia.

In my previous communication,[1] I stated that a logical explanation for the variation in response among certain groups of individuals and among the sexes is to be found in variation in the vagotonic predisposition. This predisposition seems to be less in females and in neurocirculatory asthenia. That local disease affecting the various components of the reflex vagal arc will lower the threshold of irritability of that arc, producing a heightened response, is evident. The fact that not all cases who show apparently similar disease exhibit the response seems to prove that the vagotonic predisposition is necessary in addition to a diseased state. In reviewing the literature on the oculocardiac reflex, we find that other authors seemed to have arrived at the same conclusion. Loeper and Mongeot[2] found an exaggerated oculocardiac reflex in hypervagotonic

and diminished in hypersympatheticotonic individuals. Gautrelet[3] found the oculocardiac reflex to be exaggerated in hypervagotonic individuals.

The vagotonic tendency, judging from our additional observations presented in this paper, is small in adolescence, increases in adult life, and reaches a fastigium in middle life. Individuals who are already under extreme vagal tone, such as in marked bradycardia, do not seem to respond any further to increased vagal stimulation. The existence, however, of an evident moderate vagotonic state, as shown by moderate bradycardia, predisposes to increased vagal response. A physiologic limit of vagal tone apparently exists. In arriving at this conclusion, consideration must be given to the statement of Loeper and Mongeot[4] that the oculocardiac reflex is preserved in bradycardias of nervous origin, but not of myocardial origin. They do not tell us, however, how differentiation of the two origins is made in cases of simple sinus bradycardia. Besides, our findings with the carotid sinus reflex seem to show that moderate simple sinus bradycardia accompanied by myocardial disease show a much greater tendency toward vagal response than the same forms of heart disease with a normal rate.

The arteriosclerotic heart disease group seems to show a definitely greater tendency toward increased vagal response, in cases of vagal hyperactivity, than in all other forms. This is evident from the rise in the curves of response here, in sinus bradycardia and more particularly in sinus arrhythmia. This phenomenon is hard to explain.

Summary and Conclusions. Observations on the carotid sinus reflex in a series of 345 cases showed that the response is small in adolescence, increases in adult life, and reaches a fastigium in middle life. The reflex was absent in cases of marked sinus bradycardia. In moderate bradycardia, on the other hand, the response is greatest. In tachycardia, it is greatly diminished. In arteriosclerotic heart disease, the general curve of response is higher than in the other groups, and those group with evident vagal activity, as shown by sinus bradycardia and sinus arrhythmia, responded most.

We may assume that a vagotonic predisposition is necessary to get a reflex vagal slowing of the heart by carotid sinus pressure. This predisposition progresses with age, reaching its maximum in middle life. A physiologic limit of this predisposition seems to exist, beyond which no further response is obtainable on stimulation. The constitutional state associated with arteriosclerosis heightens the vagotonic tendency.

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CLINICAL OBSERVATIONS ON THE CAROTID SINUS REFLEX.

III. The Response to Carotid Sinus Pressure in Cases With and Without Precordial Pain.

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It is fairly well established that precordial pain is in many cases due to local asphyxiation of the heart muscle caused by local blood impoverishment. The greatest amount of asphyxiation occurs in coronary occlusion where the circulation to a local area is suddenly cut off. Hence pain is greatest and most prolonged under such conditions. Of some of the recent clinical and experimental evidence tending to substantiate this theory may be mentioned the work of Sutton and Lueth[1] and of Wood, Wolferth and Livezey.[2]

That the vagus nerve has a constricting effect on the coronary vessels was shown by Panim[3] as long ago as 1858, and was repeatedly confirmed by numerous workers since, although apparently disproved by a few. Gilbert and Fenn[4] in a recent experimental study found, like others before them, that digitalis has a vasoconstrictor effect upon the coronary vessels in some animals. It is also known that some cases of angina have followed the use of digitalis. They concluded that all cases of angina probably result from reflex vasoconstriction operating from various sources. It is caused by an overlabile autonomic nervous system with lowered threshold. Greene[5] found that efferent coronary vasoconstriction occurs through the vagus and vasodilation through the sympathetic. Normal reflex vasoconstriction is relatively weaker than vasodilation, and both correspond to the range of cardiac activity. In diseased hearts the reflex coronary vascular response is not in harmony with the reflex response of the heart itself. The result is that not enough coronary vasodilation occurs to ensure a sufficient blood supply to the heart during increased effort. Local asphyxiation of the heart muscle is the result and accounts for all cases of angina. This condition may result from vasoconstriction or failure of vasodilation.

It would seem that increased vagal tone with its efferent vasoconstriction effect on the coronary system may be at least partly responsible for angina in the presence of coronary sclerosis. We often find cases on the postmortem table with marked degrees of coronary sclerosis and even calcification without any history of angina during life. In these cases there must be a sufficient blood supply to the heart to prevent cardiac asphyxiation even in the presence of coronary sclerosis. The assumption may be made here that the added factor of heightened vagal tonicity of the coronary vessels is absent.

If this theory should be correct, a heightened carotid sinus reflex response which indicates increased vagal activity or lability should be a frequent accompaniment of precordial pain. I have accordingly analyzed the series of 345 cases reported in the two preceding articles[6,7] with a view of determining the frequency of the carotid sinus reflex response in cases with and without precordial pain.

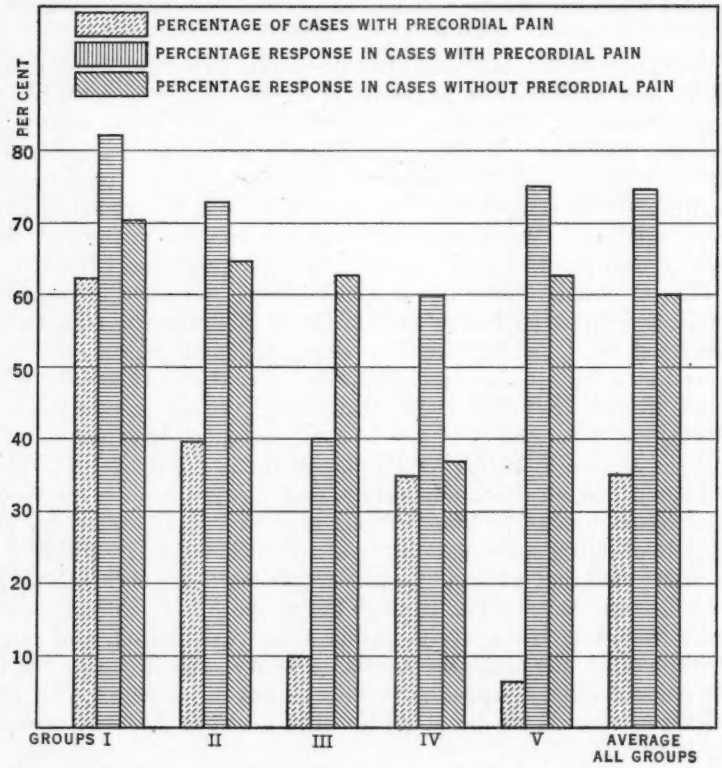

CHART I.—Percentage of cases with precordial pain and the carotid sinus reflex response in cases with and without pain.

These cases were divided according to the main diagnosis into the same five groups as in the first paper (see Table 1 of this paper). The preceding papers covered the frequency and the degree of response, in the various disease groups, among the sexes, at different ages and with various rates and rhythms of the heart. The present analysis covers the incidence of precordial pain in each group and the relative frequency of the carotid sinus reflex response in cases with and without such pain. Cases with precordial pain due to thoracic wall disease were classed under the subdivision of patients with no precordial pain.

The accompanying table and figure give a summary of the entire series of cases. We find that the percentage showing precordial

pain is greatest in the arteriosclerotic heart disease group, less in the hypertension group and least in the group with no cardiac disease, where it is almost neglible. The neurocirculatory asthenia group shows a comparatively high percentage of cases with precordial pain, while the rheumatic group shows the smallest percentage with such pain among the cardiac cases.

TABLE 1.—INCIDENCE OF PRECORDIAL PAIN AND THE CAROTID SINUS REFLEX RESPONSE IN CASES WITH AND WITHOUT PRECORDIAL PAIN.

Group.	Total number of patients.			Response of patients with precordial pain.			Response of patients without precordial pain.		
	With precordial pain.	Without precordial pain.	Percentage showing precordial pain.	Number responding.	Number not responding.	Percentage response.	Number responding.	Number not responding.	Percentage response.
I	71	44	61.7	58	13	81.7	31	13	70.4
II	22	34	39.2	16	6	72.7	22	12	64.7
III	5	45	10.0	2	3	40.0	28	17	62.2
IV	20	38	34.5	12	8	60.0	14	24	37.0
V	4	62	6.0	3	1	75.0	39	23	62.9
Total	122	223	35.3	91	31	74.6	134	89	60.0

Group I, arteriosclerotic heart disease; Group II, hypertension and hypertensive heart disease; Group III, rheumatic heart disease; Group IV, neurocirculatory asthenia, and Group V, general constitutional disease without any cardiac abnormalities. The total is the average for all the groups.

The carotid sinus reflex occurred with greatest frequency in cases with precordial pain in all groups except in the rheumatic heart disease group. The number of cases with precordial pain in this group, however, is too small to form a basis for definite conclusions. In neurocirculatory asthenia there was the greatest difference in response between those with and those without pain, as many as 23 per cent more of the cases with precordial pain responded.

Many cases that showed the greatest degree of vagal response in the arteriosclerotic group had no precordial pain. Some of these showed either effort or paroxysmal dyspnea, asthenia or more or less congestive failure as evidence of cardiac disease. Some showed no evident symptoms but the electrocardiogram was distinctly abnormal. In the group of neurocirculatory asthenia, on the other hand, the degree of response was somewhat greater in cases presenting precordial pain.

In the group with no heart disease, there were only 4 cases that showed some precordial pain and of these 3 (75 per cent) showed response. This number of cases, however, is too small for comparison with the greater number of cases in this group who had no precordial pain.

Slight precordial pain was produced by carotid sinus pressure

in very few instances where no pain was present at the time such pressure was applied. No accentuation of pain occurred if pain was present.

In the majority of cases no untoward effects of carotid sinus pressure were noticed. Several cases where the heart slowed to any marked extent complained of dizziness. Some developed a sensation of fainting, and two developed momentary unconsciousness. In a few cases there was some respiratory embarrassment, and some developed a mild coughing spell during the entire period of carotid sinus pressure.

Comment. It would seem that precordial pain may be due in some cases to increased vagal activity. The number of such cases is the difference in the number responding to carotid sinus pressure among those with and those without pain. In the arteriosclerotic group it is about 11.3 per cent, in the hypertensive group 8 per cent, in neurocirculatory asthenia it is highest, being about 23 per cent, while in the non-cardiac group it is 12.1 per cent.

Although these percentages are small they indicate that lability of the autonomic nervous system, especially that of the vagal portion, is in some way connected with the production of precordial pain at least in some instances. The work of the authors previously mentioned point to vasoconstriction of the coronary vessels with the resultant local asphyxia as the possible mode of production of pain in these cases. The number of cases in which this mechanism of pain production is operative is probably equal to that number of cases that will show the anginal syndrome under digitalis, being a vagotropic drug.

That not all cases with increased vagal tone show precordial pain, and that not all painful cases have an increased vagal tone would indicate that additional factors are concerned in the pathogenesis of precordial pain.

Summary. In a series of 345 cases it was found that the carotid sinus reflex occurs more often among patients with than without precordial pain. The greatest difference occurs in neurocirculatory asthenia. Many cases with a high degree of response had no pain, and very seldom was pain elicited or accentuated in any case by carotid sinus pressure.

The findings indicate that increased vagal activity with the resultant coronary vasoconstriction and cardiac anemia may be the cause of angina in some cases.

I am indebted to Dr. Robert H. Halsey for his valuable criticism and suggestions in the preparation of this and the preceding papers.

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REVIEWS.

CALCIUM METABOLISM AND CALCIUM THERAPY. By ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College, etc. With a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Pp. 252. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1933. Price, $2.50.

THE rapid developments in the study of calcium metabolism, both diagnostically and therapeutically, make this edition highly desirable even after the short space of two years. The chief changes from the first edition are on "the altered conception of the relationship between the parathyroid hormone and vitamin D; the relation of the calcium and phosphorus intake to the effects of vitamin D and the parathyroid hormone; the significance of phosphatases in the mechanism of ossification and in bone diseases; dental caries; the influence of calcium upon the pharmacological action of various drugs; the *in vivo* diffusibility of calcium in nephritis with uremia and in parathyroprivic tetany; the nature of parathyroid hormone action."

F. K.

EXPERIMENTAL PHARMACOLOGY AND TOXICOLOGY. By HENRY G. BARBOUR, A.B., M.D., Yale University, New Haven. Pp. 141; 14 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $2.75.

THIS book outlines a laboratory course in pharmacology for medical students. Outstanding chemical and physiological properties of important drugs are illustrated by simple, direct experiments which have proved successful in the author's extensive experience. The material is useful to the teacher of pharmacology, but it is too elementary to be of much value to the toxicologist, and there is too little coördination with physiology for the clinician seeking new information concerning drug actions.

J. R.

ESSENTIALS OF PEDIATRIC NURSING. By RUTH ALICE PERKINS, R.N., B.S., Graduate of Children's Memorial School of Nursing, etc. Pp. 467; 55 engravings and 6 full page colored plates. Second edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1932.

THE book is wide in its scope, laying particular stress upon the important subject of preventive pediatrics. It endeavors to instruct the nurse in the phases of work encountered in the home, the health center, the outpatient clinic as well as in the medical and surgical wards of the hospital. An excellent section is that devoted to the psychology and mental hygiene of the child, and to the consideration of the child as a personality as well as an example of a disease. The inclusion of valuable bibliographic material makes for great usefulness. The description of some of the medical diseases might benefit by fuller consideration and by inclusion of some of the physiologic background of these conditions. However, all information essential to the nurse is well covered. The sections on communicable diseases and aseptic nursing technique are splendid and well worth consideration by the physician. This book may be recommended as broad in vision, accurate in information, practical, and elegantly set up and illustrated.

J. S.

A TEXTBOOK OF PATHOLOGY. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1212; 652 illustrations. Fifth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, $10.00.

SINCE the first appearance of this book in 1916, the years 1923, 1927, 1930 are the only ones in which a new printing or new edition has not appeared. An enviable record, indeed, that suggests obvious comparisons with that other great Hopkins textbook, Osler's *Practice*. In this latest revision the sections on tuberculosis, syphilis, nephritis, endocarditis and endocrine disorders have been subject to the most change. Among the new material included are items on arteriolosclerosis, congenital heart disease, tularemia, postvaccinal encephalitis, agranulocytosis, ligneous thyroiditis, ostitis fibrosa and a chapter on disorders of lipoid metabolism. Many of the drawn illustrations—always an excellent feature of the book—have been replaced by photographs, a desirable substitution if, as here, the high standard can be maintained. The lung photographs (Figs. 333 to 347) are especially praiseworthy. E. K.

CLINICAL GYNECOLOGY. By C. JEFF MILLER, M.D., Professor of Gynecology, Tulane University School of Medicine; Chief of the Department of Gynecology of Touro Infirmary, etc. Pp. 560; 134 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $10.00.

THIS book is a companion volume to "An Introduction to Gynecology" (1931), in which were discussed the fundamentals of gynecology with little or no reference to therapy. In the present volume the author comprehensively sets forth his views as to medical therapy and operative treatment for gynecologic diseases. His long experience permits him to speak authoritatively and his individual preference for particular measures are strongly indicated. He has interpolated the expressed ideas of other authors and operators; these are frequently and copiously quoted and discussed, and at times disagreed with in a friendly manner. This unusual manner of presentation of the literature adds much to the interest and ease of reading the book.

The teaching in the book is modern and rational and where a personal choice is emphasized it is always soundly conservative. There is no doubt but that this volume devoted solely to therapy will be largely and warmly received. P. W.

THE SPUTUM. By RANDALL CLIFFORD, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Pp. 167; 21 illustrations, 7 colored plates. New York: The Macmillan Company, 1932. Price, $4.00.

THIS volume is well printed on good paper in clear readable type and is suitably bound for hard use. It is divided into 11 chapters, each followed by a sufficiently comprehensive bibliography. There is a 12-page index. The 11 chapters are divided into 4 sections, including general considerations, macroscopic examination, microscopic examination and the sputum in some of the more common diseases of the bronchi and lungs. The chapters dealing with the origin and significance of the various types of sputum are fairly complete. The only method given for the Gram staining of bacteria is not in very general use, but is fairly simple and probably as satisfactory as any. It would have been helpful if some space had been devoted to methods of cell staining. The importance recently ascribed to pulmonary spiro-

chetosis would seem to require more attention than the author has devoted to it. The book is well written and the material well chosen. It will be of value both to the clinician and the laboratory worker.

F. L., JR.

PRACTICAL OBSTETRICS. By P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College; Chief Obstetrician, Jefferson Medical College Hospital. Assisted by THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College. Pp. 730; 516 illustrations, including 21 colored plates. Philadelphia: F. A. Davis Company, 1932. Price, $8.00.

THIS medium-sized volume developed from the author's teaching gives a concise presentation of modern conservative obstetrics. The chapters are arranged logically to carry the students through the entire subject. For the practitioner the advice given as to treatment is rational and always conservative.

The newer ideas of the physiology of the reproductive organs are presented in an interesting manner as they relate to diagnosis and parturition. In the discussion of normal pregnancy one may question the advisability of making a vaginal examination on each return visit; on the other hand, the advice about unnecessary vaginal examinations late in pregnancy and in labor is good. For normal labor the modified Garden of Eden plan with constant alertness is advocated. For the aftercoming head the forceps of Piper is the preferred. Potter's version is beautifully illustrated, though indications for its use are lacking. For placenta previa prompt Cesarean section is urged, with transfusions if necessary.

Under obstetric analgesia-anesthesia the need for special nursing care, or crib beds, for the partly unconscious patient is not stressed. Section on the newborn is well developed. Some of the methods for resuscitation of the newborn seem obsolete. Stander's classification of the toxemias is comprehensively discussed. Fay and Arnold's dehydration treatment is described but not evaluated. The quick termination of pregnancy in progressive toxemias by abdominal hysterectomy with local anesthesia is not more than mentioned, in contrast to the recommended bougie induction of labor. In posterior occiput dystocias manual rotation and forceps are preferred; expectancy is recommended in breech cases. On the moot point of lumbar puncture in intracranial hemorrhage in the newborn, repeated taps are recommended. There is a section on obstetric jurisprudence, quite germane to the subject and seldom seen in textbooks. The appendix on referred reading is a noteworthy addition.

The book is well adapted to students for the definite and clear presentation given, the succinct paragraphs on pathology, complications and treatment will appeal to the general practitioner, as will also the generally conservative tone of the book.

P. W.

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 182; 26 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $2.75.

THIS short text in physical chemistry covers only those topics that are important for students in physiology and medicine. These include such fundamental subjects as the gas laws, the laws of solution and the colloidal state, followed by chapters of more immediate physiologic interest on equilibria in blood, enzyme action and oxidation-reduction potentials.

The latter chapters will be useful to many investigators in related fields because of the recent rapid growth of these subjects. The present Reviewer has found them presented in a clear and readable manner. For the student there are lists of questions at the end of each chapter and a bibliography of original papers and texts for further reading. A good feature is brief biographical sketches in footnotes of important physical chemists. Use of this book does not require knowledge of higher mathematics.

M. McC.

CHILDREN'S TONSILS IN OR OUT. By ALBERT D. KAISER, M.D., Associate Professor of Pediatrics, University of Rochester Medical School. Pp. 307; 25 illustrations. Philadelphia: J. B. Lippincott Company, 1932. Price, $5.00.

THE author's carefully conducted researches in this field qualify him eminently for writing a book of this kind. It represents the results of a 10 year's study involving nearly 5000 children, and planned particularly to secure data on the value of tonsil and adenoid operations. The need for such a book is apparent to the practising physician, who, with his colleague the laryngologist, is often perplexed as to whether operation shall or shall not be performed. Controlling his observations by comparing groups of children with similar conditions, half of whom had had the advised operation, and half of whom did not, the author has considered the relations of tonsils and adenoids to common colds, tonsillitis, laryngitis, cervical adenitis, otitis, sinusitis, bronchitis as well as many general conditions such as scarlet fever, rheumatic disease, nephritis and pyelitis. There are chapters on the history of tonsillectomy, the anatomy, physiology and bacteriology of the tonsils, the symptoms of pathologic tonsils and adenoids, the hazards of tonsillectomy, on incomplete tonsillectomy, on radiation therapy and on electrosurgery of the tonsils. The final chapter summarizes the evidence and on that basis presents the indications for and the contraindications to tonsillectomy. This book should find a welcome reception by those concerned with the health of children. It is attractively printed in good-sized type on a dull-finished paper.

J. S.

ORAL SPIROCHETES AND RELATED ORGANISMS IN FUSOSPIROCHETAL DISEASE. By DAVID T. SMITH, A.B., M.D., Associate Professor of Medicine Duke University School of Medicine, Durham, N. C. Pp. 243; 53 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $4.50.

THIS valuable monograph on the fusospirochetal infections of man is not of interest to the stomatologist alone as the title might indicate at first glance. Spirochetal bronchitis, bronchiectasis, lung abscess and pulmonary gangrene are dealt with clearly from a clinical and laboratory point of view, with the statement that spirochetes are probably the most frequent of serious pulmonary invaders in chronic non-tuberculous processes. The possible relation of fusospirochetal infection to agranulocytic angina, infectious mononucleosis, and pseudoleukemia is briefly discussed. The author suggests a possible rôle for these organisms in Ludwig's angina, amebic dysentery, and focal infection from oral sources. Fusospirochetal dysentery, appendicitis, laryngitis, tropical ulcer and genital infections are given separate chapter headings. Considerable fault can be found with the chapter on pyorrhea alveolaris. The morphology and biology of the oral spirochetes and associated bacteria are well discussed. It seems unfor-

tunate that the oral protozoa were not described. Experimental and clinical evidence is presented that the following four organisms must be in symbiotic relationship to produce most clinical pictures; a spirochete, a fusiform bacillus, a vibrio, and a streptococcus. Cultural evidence indicates that fusiform bacilli are dissociated forms of spirochetes. The bibliography lists 822 references. H. H.

AMERICAN AND CANADIAN HOSPITALS. A Reference Book edited by JAMES CLARK FIFIELD, with the coöperation of the American Hospital Association. Pp. 1560; 1 colored illustration. Minneapolis: Midwest Publishers Company, 1933. Price, $10.00.

THIS highly useful book, fostered by the American Hospital Association, contains short accounts of the history and present status and statistics of all the hospitals of the United States and Canada. As far as we have been able to test the matter, its content is accurate, inclusive, pertinent and up to date. As a work of reference it should be invaluable to those seeking information of this kind. A 58-page Appendix contains considerable information about institutions concerned with hospital work. E. K.

STREPTOCOCCI IN RELATION TO MAN IN HEALTH AND DISEASE. By ANNA W. WILLIAMS, M.D., First Assistant Director, Bureau of Laboratories, Department of Health, City of New York. Pp. 260; 7 plates, 1 illustration and 19 tables. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

DR. WILLIAMS is to be congratulated upon the production of this very readable monograph. It is complete without being cumbersome. To those engaged in the general or special practice of medicine it can be wholeheartedly recommended as a thorough review of a subject which is of great practical importance. As a conservative exposition of the progress which has been made in a field where much loose thinking has from time to time been exploited, it should be of great service in the avoidance of faddism. Particularly valuable is the conservative attitude toward serum and vaccine therapy. The research worker, who is conversant with the present need for progress in the knowledge of streptococci and streptococcal disease, will welcome, from one of the leading investigators in the field, this summary of past and present accomplishment; although he may feel some disinclination to agree with the identification of endotoxin with specific agglutinogen. To him, many problems for future inquiry will be suggested by the merciless exposition of existent gaps in our knowledge.

It is unfortunate that a work of such high quality should be marred by numerous typographical errors of omission and commission. C. H.

MODERN ALCHEMY. By WILLIAM ALBERT NOYES, University of Illinois, and W. ALBERT NOYES, JR., Brown University. Pp. 207; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.00.

THE Preface of this book contains the following: "For more than a thousand years alchemists sought in vain for the Philosopher's Stone, which should transmute base metals into gold and for an Elixir of Life, which should give eternal youth. The quest was finally abandoned as hopeless, but the transmutation of elements has been observed in recent

times and many ways of healing disease and prolonging life have been found. The vicissitudes of the search for transmutation and for healing principles are typical of the progress of science and have been taken as the groundwork of this book. In the first chapter, there is a superficial survey of the various branches of science and an attempt is made to discover their common characteristics. This is followed by an outline of modern ideas about the constitution of matter, given as an illustration of the scientific method in dealing with one of the most fundamental problems engaging the attention of scientific men and as a basis for the discussion of valence."

There are thus discussed the methods of science, atomic structure, the transmutation of the elements, the philosopher's stone, valence, the effect of various radiations on chemical systems, new elements and new uses for old ones, the elixir of life.

The authors are well known Professors of Chemistry who have presented in readable form subjects of major importance to the progress of medicine.

B. L.

GROWTH. By the LATE JAMES LORRAIN SMITH, M.D., LL.D., D.Sc., F.R.S., Professor of Pathology, University of Edinburgh. Edited by J. S. HALDANE, C.H., M.D., F.R.S. Pp. 131; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 6/- net.

AN understanding of "Growth," the creative principle of the body would go far toward supplying an understanding of life itself, to say nothing of such important diseases as carcinoma and sarcoma. The present small and inexpensive but attractive volume gives Lorrain Smith's thoughts on these subjects. An introduction and 14 chapters had been practically finished before his death. The imperfect sketches of other chapters have been omitted and a supplementary chapter added by the author. Growth and size as expressed by increase in number of cells and occasionally in size of cells, the difference of fish growth from mammalian growth, why repair stops when the original size is restored, why liver—though existing in amounts more than needed—"is rigidly restored to the full amount" after partial destruction—such topics indicate the interest that one expects to derive from perusal of this thoughtful effort.

E. K.

ELEMENTS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By LOUIS N. KATZ, A.M., M.D., Physiologist and Director of Cardiovascular Research, The Michael Reese Hospital, Chicago; Assistant Professor of Physiology, The University of Chicago, and VICTOR JOHNSON, PH.D., Instructor in Physiology, The University of Chicago. Pp. 39; 38 plates. Chicago: The University of Chicago Press, 1932. Price, $1.00.

THIRTY-EIGHT excellent electrocardiograms (one to a page), illustrating 36 different deviations from the normal, comprise the body of this useful booklet. With the exception of a short preface, a table of characteristics of the normal electrocardiographic cycle and a very practical appendix ("Procedure in reading an electrocardiogram"), the rest of the text consists of copious legends to each figure. The book obviously and admittedly omits consideration of the *raison d'être* of the electrocardiogram and of all but the electrocardiographic phases of cardiology. However, as an auxiliary to more comprehensive efforts it covers the field indicated in its title so excellently, that it may be enthusiastically recommended to the non-specializing internist and the beginning student of cardiac physiology for whom it has been prepared.

E. K.

ELEKTROKARDIOGRAPHIE FÜR DIE AERZTLICHE PRAXIS. Vol. 14 of Medizinische Praxis, Sammlung fur Aerztliche Fortbildung. Herausgegeben von L. R. Grote, A. Fromme, K. Warnekros. By PROF. DR. ERICH BODEN, Direktor der Med. Poliklinik der Med. Akademie, Düsseldorf. Pp. 161; 91 illustrations (some colored). Leipzig: Theodor Steinkopff, 1932. Paper, Rm. 12; Cloth, Rm. 13.50.

LIKE several books on clinical electrocardiography in English that have been reviewed in these columns, these 14 lectures cover first the underlying principles of electrocardiography in health and disease (5 lectures), and next in more detail the practical applications, with inclusion of typical case reports (9 lectures). Especially praiseworthy are the diagrammatic drawings of the opened heart, accompanying the appropriate electrocardiograms. Bundle branch and arborization block are considered in the lecture on myocardial disease and in the former the older nomenclature is retained.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Dietetics for the Clinician. By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, in Collaboration with RUTH LOTHROP GALLUP, Dietitian. Foreword by HERMAN O. MOSENTHAL, A.B., M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University. Pp. 666; 31 tables. Philadelphia: Lea & Febiger, 1933. Price, $6.50.

Light Therapy. By FRANK HAMMOND KRUSEN, M.D., Director of the Department of Physical Medicine, Temple University School of Medicine, Philadelphia. Foreword by JOHN A. KOLMER, M.D., DR. P.H., D.SC., LL.D., Professor of Medicine, Temple University School of Medicine. Pp. 196; 33 illustrations. New York: Paul B. Hoeber, Inc., 1933. Price, $3.50.

Intracranial Tumors. By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. Pp. 475; 157 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $6.00.

Operative Surgery. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (ED.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (ED. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 590; 321 illustrations. New York: Oxford University Press, 1933. Price, $5.25.

Practical Hematological Diagnosis. By O. H. PERRY PEPPER, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and DAVID L. FARLEY, M.D., Physician to the Pennsylvania Hospital, Philadelphia, and to the Cooper Hospital, Camden, N. J.; Associate in Medicine at the University of Pennsylvania. Pp. 562; 3 plates of colored illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $6.00.

The Nervous Child at School. By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Physician in Charge of the Children's Department, Guy's Hospital. Pp. 160. New York: Oxford University Press, 1933. Price, $1.50.

Proceedings of Meetings of the New York Pathological Society, 1932. Pp. 53; 6 illustrations.

Binocular Vision and the Modern Treatment of Squint. By MARGARET DOBSON, M.D. (LOND.), Ophthalmic Surgeon to the New Sussex Hospital for Women and Children, Brighton; Oculist in Charge of the Kilburn (L.C.C.) Eye Clinic. Pp. 107; 32 illustrations. New York: Oxford University Press, 1933. Price, $2.75.

The Physio-chemical Theory of the Process of the Internal Defence of Animals. (A Preliminary Report.) By DAVID SATY ANAND, M.B., B.S., House Physician, Infectious Diseases Hospital, Lahore, India. Pp. 91. Anarkali, Lahore: P. R. B. S. Press, 1933.

Surgical Anatomy. By C. LATIMER CALLANDER, A.B., M.D., F.A.C.S., Assistant Clinical Professor of Surgery and Topographic Anatomy, University of California Medical School; Associate Visiting Surgeon to the San Francisco Hospital. With a foreword by DEAN LEWIS, M.D., Sc.D., LL.D., F.A.C.S. Pp. 1115; 1280 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price $12.50.

Operative Surgery, Vol. VII. The Newest Operations, General Index to Complete Work, Vols. I–VII. By WARREN STONE BICKHAM, M.D., and PHAR.M. (TULANE), M.D. (COLUMBIA), F.A.C.S., Junior Surgeon to Touro Hospital, New Orleans; Fellow of the New York Academy of Medicine, etc., and CALVIN MASON SMYTH, JR., B.S., M.D., F.A.C.S., Assistant Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Surgeon-in-Chief, Methodist Episcopal Hospital; Visiting Surgeon, Abington Memorial Hospital. Pp. 849; 765 illustrations. Philadelphia: W. B. Saunders Company, 1933. Price, $10.00.

The Surgical Clinics of North America. Vol. 13, No. 2 (New York Number, April, 1933). Pp. 274; 56 illustrations. Philadelphia: W. B. Saunders Company, 1933.

A System of Bacteriology in Relation to Medicine, Vol. VI. Immunity. By various authors. Pp. 537; illustrated with charts and tables. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.

Roentgenographic Studies of the Urinary System. By WILLIAM E. LOWER, M.D., F.A.C.S., Chief of Department of Urology, Cleveland Clinic; Former Associate Professor of Genitourinary Surgery, Western Reserve University; Surgeon to Cleveland Clinic Hospital, and BERNARD H. NICHOLS, M.D., F.A.C.R., Chief of Department of Roentgenology, Cleveland Clinic. Pp. 812; 812 illustrations. St. Louis: The C. V. Mosby Company, 1933. Price, $16.00.

The Physiological Effects of Radiant Energy. By HENRY LAURENS, PH.D., Professor of Physiology in the Tulane University School of Medicine. Pp. 610; 104 illustrations. New York: The Chemical Catalog Company, Inc., 1933. Price, $6.00.

Manuscripta Medica. A Descriptive Catalogue of the Manuscripts in the Library of the Medical Society of London. By WARREN R. DAWSON, F.R.S.E., F.R.S.L., F.S.A. (SCOT.), Fellow of the Royal Society of Medicine (Vice-President, Section of History); Honorary Research Assistant, Department of the History of Medicine, University College, London; Honorary Librarian of Lloyd's. Pp. 140. London: John Bale Sons & Danielsson, Ltd., 1932. Price, 15s.

The International Medical Annual, Fifty-first Year, 1933. A Year Book of Treatment and Practitioner's Index. By various contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P. (the late), and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 572; 98 illustrations and 61 plates, some colored. Baltimore: William Wood & Co., 1933. Price, $6.00.

It maintains its high grade of reporting current advances, and the illustrations are especially praiseworthy.

Kreislaufstörungen und Pathologische Histologie. By PROFESSOR DR. MARTIN NORDMANN, Privatdozent für allgemeine Pathologie und spezielle pathologische Anatomie an der Universität Tübingen. Band IV. Ergebnisse der Kreislaufforschung. Monographien aus dem Gebiete Beschreibender, Experimenteller und Klinischer Kreislaufforschung. Herausgegeben von DR. MED. BRUNO KISCH, Ord. Professor der Physiologie an der Universität Köln. Pp. 174; 14 illustrations. Leipzig: Theodor Steinkopff, 1933. Price: Paper, Rm. 13.50; Cloth, Rm. 15.00.

Sécrétion Interne et Régénérescence. By DR. N. E. ISCHLONDSKY. Pp. 336; 72 illustrations. Paris: G. Doin & Cie., 1933. Price, 90 fr.

Lymphatics, Lymph and Tissue Fluid. By CECIL K. DRINKER, B.S., M.D., Professor of Physiology, Harvard School of Public Health, and MADELEINE E. FIELD, A.B., PH.D., Instructor in Physiology, Harvard School of Public Health. Pp. 254; 11 illustrations and various tables. Baltimore: The Williams & Wilkins Company, 1933. Price, $3.00.

History of Urology. In Two Volumes. Prepared under the Auspices of the American Urological Association. Editorial Committee: EDGAR G. BALLENGER, WILLIAM A. FRONTZ, HOMER G. HAMER, BRANSFORD LEWIS, Chairman. Pp. 746; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $8.00 set.

NEW EDITIONS.

Peptic Ulcer. By JACOB BUCKSTEIN, M.D., Instructor in Gastrointestine Roentgenology, Cornell University Medical College; Associate Attending Gastroenterologist, Sydenham Hospital, etc. Vol. 10 of Annals of Roentgenology, Edited by JAMES T. CASE, M.D., Professor of Radiology, Northwestern University Medical School. Pp. 417; 411 illustrations. Second edition revised and enlarged. New York: Paul B. Hoeber, Inc., 1933. Price, $12.00.

A Companion to Manuals of Practical Anatomy. By E. B. JAMIESON, M.D., Senior Demonstrator and Lecturer on Anatomy, University of Edinburgh. Pp. 654. Third edition. New York: Oxford University Press, 1932. Price, $5.00.

Clinical Aspects of the Electrocardiogram. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Lying-in Hospital and Woman's Hospital, New York City. Pp. 295; 74 illustrations. Third edition, revised. New York: Paul B. Hoeber, Inc., 1933. Price, $5.50.

Surgical Operations. A Textbook for Students and Nurses. By E. W. HEY GROVES, M.D., B. Sc., M.S., F.R.C.S., Consulting Surgeon, Bristol General Hospital; Emeritus Professor of Surgery, University of Bristol, etc. Pp. 263; 204 text illustrations and 37-page Appendix of illustrations of instruments. Third edition. New York: Oxford University Press, 1933. Price, $4.50.

A third edition is evidence that a book has well filled a certain need. The operative set-up, instruments, position of the patient, preparation of the part and stages of the operation are briefly given. In the appendix the more commonly used instruments are illustrated. The printing and illustrating of this book are superior to those found in most textbooks for nurses. I. R.

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On the Etiology and Pathogenesis of Whooping Cough.—That the Bordet-Gengou bacillus is the specific causal organism responsible for whooping cough is by no means a settled question, as shown by a recent paper by RICH (*Bull. Johns Hopkins Hosp.*, 1932, **51**, 346). The author discusses first Mallory's original work and that of other authors who have proved that the evidence of the specificity of this organism is not at all conclusive, and that it is quite possible that the cough of pertussis may be provoked by organisms other than the specific bacillus whose implication in the cilia of the respiratory tract is responsible for the paroxysmal cough. He shows that it may be possible to reproduce the whooping cough syndrome with cultures of influenza bacilli and that the influenza organism may be entangled in the cilia of the air passage in exactly the manner in which the Bordet-Gengou bacillus localizes. He discusses other features of whooping cough which may be reproduced likewise in other diseases. For example, the mononuclear cell infiltration of bronchial walls which occurs in whooping cough uncomplicated by pneumonia is characteristic of interstitial pneumonia. This pathologic picture occurs almost exclusively in those diseases which are believed to be due to filterable viruses, as for example, measles, influenza or whooping cough. The suggestion is advanced by the author that the lesion of whooping cough may be the result of, or may be produced by an invisible virus rather than by secondary bacterial invaders. He suggests, furthermore, that many of these observations indicate that the invisible virus may play an important rôle in the etiology of whooping cough and he demonstrates instances in which internuclear inclusion bodies in the lungs occurred in cases of whooping cough. These may possibly represent the effect of aspirated herpes virus.

The Prognosis in Cardiac Disorders.—An optimistic and cheerful presentation of the prognosis of the various types of heart disease has been presented by RUDOLF (*Canadian Med. Assn. J.*, 1933, **28**, 35). He discusses first disturbances of cardiac rhythm and points out much that is well known, but to be accentuated is the statement that extrasystoles in the absence of other signs of heart disease mean but little. In organic heart disease the statement is made that occasionally subacute bacterial endocarditis is cured, although it is usually fatal within a few months. In syphilitic heart disease gotten early, the outlook is

fairly good if the specific treatment is thorough. In the tertiary cases, death usually occurs within 5 years after heart symptoms have set in, a really rather remarkably hopeful prognosis in this condition. The patient with angina pectoris may die from the disease, but not in the first attack, and the majority of sufferers do not die in an attack, but from subsequent heart failure. Quite commonly if the cause of the anginal attack is discovered, it can be controlled and the patient may go on for some years. With coronary thrombosis most cases are unrecognized, judging from pathologic studies, but in the more severe cases with recognizable symptoms, a larger artery being implicated, the prognosis is extremely grave. He concludes with this word of advice: "A gloomy view may precipitate heart failure when otherwise this might have been long deferred. Many a cardiac hypochondriac owes his condition largely to some indiscreet, and the often quite unwarranted, opinion expressed by an over-anxious medical attendant."

SURGERY

UNDER THE CHARGE OF

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Iodin in Hyperthyroidism.—Iodin in some form or other has been used for the treatment of goiter since ancient times. In recent years NEISSER (*Klin. Wchnschr.*, 1920, **57**, 461) stressed the value of potassium iodid in the treatment of exophthalmic goiter and LOEWY and ZONDEK (*Deutsch. med. Wchnschr.*, 1921, **47**, 1387) showed quite conclusively its effect on the lowering of the basal metabolic rate. However, the impetus for the use of iodin in the treatment of thyrotoxicosis followed the work of PLUMMER and BOOTHBY (*Col. Papers of the Mayo Clinic and the Mayo Foundation*, 1923, **15**, 565; *J. Iowa State Med. Soc.*, 1924, **14**, 66). These authors presented data on 400 cases of hyperthyroidism treated by large doses of iodin which corroborated the findings of Loewy and Zondek in regard to the effect of iodin in reducing the respiratory exchange. In most of the earlier work on patients as well as the work on experimental animals in regard to the hyperthyroid state, the iodin was administered in the form of potassium iodid. Plummer and Boothby, however, advocated the use of Lugol's solution instead of potassium iodid "because it is an aqueous solution of iodin and potassium iodid and therefore provides a large amount of iodin loosely combined with potassium." The inference that Lugol's solution is more useful than potassium iodid in the treatment of hyperthyroidism has been rather generally accepted as a fact in this country. In addition the statement quoted above connotes that large doses of iodin are needed. The data presented by THOMPSON, COHEN, THOMPSON, THORP, and BRAILEY (*Arch. Int. Med.*, 1930, **45**, 430) refute this idea

since these workers were able to produce as great a fall in the basal metabolic rate with small doses of Lugol's solution as with large doses.

LERMAN and MEANS (*Am. J. Med. Sci.*, 1931, **181**, 745) compared the effect of Lugol's solution, potassium iodid and ethyl iodid as to the effect on the basal metabolic rate in exophthalmic goiter and found all equally effective. These results indicate that the type of iodin compound administered makes little difference. Inhalations of ethyl iodid were as effective in reducing the metabolic rate as solutions of inorganic iodin compounds given by mouth.

COHN (*Arch. Int. Med.*, 1932, **49**, 950) studied the rate of absorption of iodin from various portions of the gastro-intestinal tract and found that iodin was absorbed readily from all portions of the intestine. He also found that whether iodin was introduced as free iodin, Lugol's solution, or potassium iodid the solutions recovered from the intestine never gave a test for free iodin when allowed to remain in the intestine for as long as 4 minutes. These results explain why Lugol's solution is no more efficacious in alleviating the symptoms of thyroid disease than potassium iodid, since the free iodin in Lugol's solution is converted to iodid before absorption. Since Lugol's solution is more unpleasant to take there appears little rationale in its use in preference to potassium iodid. That free iodin is rapidly converted to iodid in the gastro-intestinal tract is not a new observation since this fact has been stated repeatedly in standard pharmacological textbooks. The studies of Cohn reëmphasize the rapidity of this conversion. The continued use of iodin solutions over a long period of time in the treatment of hyperthyroidism has been largely responsible for the delay in accepting this efficacious agent for the preparation of patients for thyroidectomy. Shortly after the discovery of iodin by COURTOIS (*Ann. de Chim. et Physiol.*, 1813, **88**, 304), COINDET (*Ibid.*, 1820, **15**, 49) introduced the use of iodin in the treatment of goiter, but due to the appearance of symptoms which we now understand as the result of overdosage the treatment was discontinued. MARINE (*Medicine*, 1927, **6**, 127), FRAZIER and MOSSER (*Ann. Surg.*, 1929, **89**, 849) and MOSSER (*Surg., Gynec. and Obstet.*, 1928, **47**, 168) explain the untoward effects of continued administration on the basis that in hyperthyroidism, iodin causes an increase in the amount of colloid in the acini, distending the acini, and for a time the metabolic rate decreases as a result of "pressure retention," and later increases as the stage of exhaustion ensues.

THERAPEUTICS

UNDER THE CHARGE OF
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Synthetic Preparations in the Treatment of Malaria.—MÜHLENS (*München. med. Wchnschr.*, 1932, **79**, 537) discusses malaria therapy in the light of recent advances in chemotherapy. The therapeutic

use of *plasmochin* (n-diethylamino-isopentyl-8-amino-6-methoxy-chinolin) and *atebrin* (a derivative of alkylamino-acridin) is particularly emphasized. The use of plasmochin in tropical malaria due to gametocytes and in cases with quinin idiosyncrasy is particularly indicated. Its beneficial effect in the tertian form is probably as great as, and in the quartan form probably greater than, that of quinin. In the treatment of larger groups of the population in the tropics the combination of quinin and plasmochin, in the form of tablets, each containing 0.3 gm. of quinin + 0.01 gm. plasmochin (*chinoplasmin*) proved to be very effective. In severe cases administration of 4 to 5 tablets daily up to 21 days usually eradicates the infection, and administration of after-treatment is not necessary. The author claims that chinoplasmin proved to be a most efficacious agent in prophylaxis; 1 tablet is usually taken in the evening. Cyanosis and epigastric pain are observed with relatively larger doses. The author treated 122 cases of malaria with *atebrin* and with a combination of atebrin and plasmochin. The dosage varied. Usually 0.1 gm. of atebrin was given, three times daily, for 3 to 10 days. In some instances, after 4 days without medication, treatment was reinstated. The total amount administered usually did not exceed 4.8 gm. Cases with all three types of malaria responded to atebrin. Relapses occurred but seldom. Tropical malaria due to ringform parasites did not improve, as a rule, following the administration of atebrin. In such cases quinin was administered intramuscularly for 2 days in addition to the combined administration of 0.1 gm. of atebrin and 0.01 gm. of plasmochin, three times daily. Atebrin was well tolerated by patients with quinin idiosyncrasy and with blackwater fever. Atebrin causes yellowish discoloration of the skin. This is not due to liver damage but to the liberation of acridin.

PEDIATRICS

UNDER THE CHARGE OF
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Kernikterus: Jaundice of the Nuclear Masses of the Brain.—ZIMMERMAN and YANNET (*Am. J. Dis. Child.*, 1933, **45**, 740) point out that the pathogenesis of kernikterus is that following some injury; the nerve cells are subsequently stained with the bile pigments carried to them by the blood stream. This differs in no way from the well-known fact that any intravital dye will localize in zones of injury and will leave unstained tissues that are undamaged. It was also noted that injured myelin sheaths become jaundiced. This is a further substantiation of the theory mentioned. The question arises as to why the jaundice localizes in the central nuclear masses and so rarely in the cerebral cortex. The final answer to this question is not possible at this time. However, it must be noted that the macropscopic observations on the localization of the jaundice are not absolutely accurate, for, microscopically, isolated nerve cells in both the cerebral and cerebellar cortex are found to contain bile pigment. The gross localization of jaundice

in the basal ganglia suggests close relationship between kernikterus and Wilson's disease. These two conditions have a striking similarity as regards the localization of the cerebral changes, their frequent association with hepatic lesions and the strong familial tendency. On the other hand, Wilson's disease is one of adult life rather than of childhood. There is little in the history of patients suffering with this disease to indicate a lesion existing from infancy. Although jaundice may be present, the basal ganglia are never pigmented. Clinically the symptoms are predominantingly those referable to lesions in the basal ganglia, even in those cases which have a picture suggestive of a more widespread cerebral involvement such as pseudosclerosis. In contrast to this, the cases which are diagnosed clinically as kernikterus but in which recovery occurs with sequelæ, show not only symptoms referable to lesions of the basal ganglia but also symptoms of a more diffuse cerebral involvement. The hepatic changes observed in Wilson's disease are in the nature of a fibrosis or cirrhosis, but there is little similarity in this regard in kernikterus. In 2 cases included in this report B. coli was found in the blood. Other observers have reported cultural findings. In some cases it has been impossible to show infection, but this may be due to too few blood examinations being made, and the blood should be arterial rather than venous as blood cultures of venous blood are often inconclusively negative as the bacteria may be filtered out through the capillary bed. In 1 of the cases there was evidence of umbilical and hepatic infection although the blood cultures were negative. In the fatal cases of kernikterus no definite clinical picture was seen whereby the condition could be diagnosed during life. An appreciable percentage of the cases that reveal symptoms of icterus gravis show that they may be taken as indicative of involvement of the central nervous system, such as convulsions, spasticity, irregularity of respiration, drowsiness, circulatory instability and vomiting. Of these only a small percentage show kernikterus postmortem. On the other hand, a certain percentage of newborn infants in whom jaundice of the nuclear masses of the brain is demonstrated at autopsy, have revealed during life no definite evidence that might suggest specific involvement of the central nervous system.

Aspects of Phenobarbital Poisoning.—WEIDEMANN (*Monatschr. f. Kinderh.*, 1933, **55**, 307) gives the clinical history of a girl aged 3 years, who 9 months before had suffered from measles with a severe bluish exanthem. When the child came under observation, it had had whooping cough for 4 weeks, and had been under treatment with phenobarbital 16 days. For 12 days she had received 4 tablets a day, or a daily supply of 0.06 gm. Then the treatment was discontinued because suddenly the temperature increased to 102.2° F., vomiting began, the pharynx was reddish and the entire body became covered with a light red exanthem. The physician in charge diagnosed the condition as scarlet fever and administered scarlet fever streptococcus serum. In spite of this the exanthem became more severe within the next 2 days, and the general condition became poorer. On the basis of the history and of the clinical manifestations during the first few days, measles as well as scarlet fever were excluded. Phenobarbital intoxication was suspected because the cutaneous manifestations resembled those that have been

observed as the result of another barbituric acid preparation. The incubation period of 8 to 12 days noted in this case resembled that seen in barbituric acid intoxication and the same may be said of the blood picture. Unusual aspects of this disturbance are the mucous membrane manifestations, the extraordinarily large lamellar desquamation and the protracted persistence of the cutaneous manifestations. In this case remainders of the exanthem in the form of pale brownish pigmented spots were visible after 6 months.

The Injection of Maternal Blood in Severe Vomiting of Nurslings.—AUDÉOUD (*Rev. franç. de pediat.*, 1932, **8**, 737) followed this method of treatment in 8 cases. The ages of the patients varied from 5 weeks to 3 months. All presented repeated, abundant, projectile vomiting, had lost considerable weight and were weak and in poor general condition. Injections of 20 cc. of the maternal, or sometimes of the paternal blood, were made every 2 or 3 days by injecting 10 cc. into each buttock. The treatment lasted from 3 to 9 weeks. The initial constipation was gradually replaced by normal bowel movements, the vomiting was gradually cured, and the infants regained the appearance of good health and were able to take normal meals. The increase in weight varied from 650 gm. in 22 days to 1515 gm. in 7½ weeks, the average gain being 1029 gm. Dietetic therapy should be concurrent with the hemotherapy. At first only carbonated water was given in teaspoonful doses but later it was mixed with condensed milk. The amounts were gradually increased as the vomiting subsided. Massage with warm camphor liniment and warm compresses on the gastric region every 2 or 3 hours assisted in calming the violent contractions of the stomach. The mode of action of the injections is not known but the action may be as in anaphylactic diseases.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Pyodermia Gangrenosum.—The term pyodermia gangrenosum implies a suppurative destructive process of the skin dependent upon infections of long duration elsewhere in the body. Such a case of unusual severity, secondary to infection of the gall bladder and urinary tract and progressing to fatal issue is reviewed by LANE and STROUD (*Arch. Dermat. and Syph.*, 1933, **27**, 460). A number of examples have been reported following ulcerative colitis. The primary lesions of the skin are pustules, papules or small nodules which tend to form undermined deep-seated ulcers. The causative organism appears to be a hemolytic staphylococcus albus and a streptococcus acting in symbiosis. Inocu-

lation of these organisms into rabbits has produced analogous cutaneous ulceration. The treatment should be directed principally toward the eradication of the underlying infection. Pyridium paste exerted a favorable local effect on the ulcers in the case studied by the authors.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Morphology of Genital Epithelia.—The discussion relative to the pathogenesis of endometriosis continues to be a live topic and although Sampson's theory of transtubal transplantation has enjoyed much support it is by no means universally accepted. One of the most insistent opponents to this theory is NOVAK (*Am. J. Obst. and Gynec.*, 1932, **24**, 635) who has presented a paper in which he describes the occurrence of certain differentiation anomalies in the epithelium of the various segments of the genital canal. Among them are the occurrence in the tube, of definite endometrial tissue; the occurrence in the ovary of either an endometrial or tubal type of tissue, and even, on the ovarian surface, of stratified squamous areas; the occurrence in the endometrium of either squamous areas or of patches of tubal epithelium; and finally the frequent presence in the normally columnar cell regions of the cervix of stratified squamous "metaplasia" and the occasional presence of a tubal type of epithelium. He believes that such anomalies illustrate the tendency toward intermutability of these genital epithelia under certain conditions, a tendency obviously dependent upon their common origin from the same mother tissue, the celomic epithelium. Cognizance of this fundamental fact must be taken in the interpretation of many pathologic lesions, such as endometriosis where direct transformation of germinal epithelium into either a tubal or endometrial type can be demonstrated histologically, so that it seems to the author unnecessary to invoke the doctrine of implantation in explaining this lesion.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Is Retinitis Pigmentosa Due to Vitamin Deficiency.—LEVINE (*Arch. Ophthal.*, 1933, **9**, 453) reviews the literature on retinitis pigmentosa and cites the main facts that are known about the disease. To date it

has remained practically incurable. Heredity seems to be an important factor in its etiology. It is characterized essentially by a primary degeneration of the neuroepithelium and the pigment epithelium of the retina. Its outstanding symptom is night blindness.

The most specific tissue change in vitamin A deficiency is damage to epithelial structures. One of its symptoms is night blindness. Cases of idiopathic night blindness with peculiar white dots in the fundus are reported to have cleared up on vitamin A therapy. It has been demonstrated that the retina contains more vitamin A than any other tissue except the brain and that this is located especially in the region of the rods which are particularly affected in retinitis pigmentosa. However, it has not been demonstrated as yet that the retina, in cases of retinitis pigmentosa, is deficient in vitamin A. The histology of the retina has not been studied in cases of night blindness associated with xerosis or keratomalacia (vitamin A deficiency), or in the idiopathic cases with white dots in the retina. Pillat has found pigmentation of the conjunctiva in patients with vitamin A deficiency. This has not been demonstrated in retinitis pigmentosa. For the last 5 years, the author has given large doses of cod liver oil to all his patients with retinitis pigmentosa. He was at first encouraged by the apparent improvement in vision and enlargement of the visual fields. But the improvement has not been maintained. If retinitis pigmentosa is, after all, due to vitamin deficiency, it may be that the diseased retina cannot utilize vitamin A supplied in the form of liver and cod liver oil.

OTO-RHINO-LARYNGOLOGY

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Asymmetry of the Nares. A Positive Diagnostic Sign or Entity Establishing Anatomic Displacement of Lower End of Cartilaginous Nasal Septum.—In these days when medicine's ancillary and cognate sciences are in the saddle, there is a seemingly irresistible urge to apply basic academic truths to knotty clinical problems in otolaryngology. For instance, there is a geometric proposition that, when a perpendicular is dropped from the apex of an isosceles triangle to its base, the original triangle is divided into two similar or symmetrical triangles; and that if the base of this perpendicular is moved to either side, then these two similar triangles become dissimilar or asymmetrical. Viewing the base of the nose as an isosceles triangle, and the normally situated septum as the perpendicular, METZENBAUM (*Arch. Otolaryngol.*, 1932, **16**, 690) applies this geometric proposition, and its converse, to commonly encountered dislocations of the lower end of the cartilaginous septum, and evolves therefrom a clinical principle and several corollaries. Inasmuch as many of these septal mal-alignments result from injuries sustained in infancy or childhood, and inasmuch as their simple reduction can be accomplished soon after the trauma, the importance of their early recognition is too obvious to require further comment here.

RADIOLOGY

UNDER THE CHARGE OF

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Calcification of the Suprarenal Glands in Addison's Disease.—Roentgenologic evidence of calcification of the suprarenal glands in cases of Addison's disease has been presented in numerous isolated case reports, but the frequency with which such evidence can be obtained has not heretofore been determined. Accordingly, CAMP, BALL and GREENE (*Am. J. Roent. and Rad. Ther.*, 1932, **28**, 594) have tried to determine: (1) The incidence of calcification in a series of suprarenal glands removed at necropsy in cases of Addison's disease; (2) the incidence of calcification in the suprarenal areas in a consecutive series of patients affected with Addison's disease. The suprarenal glands were obtained in 34 cases which had been listed by the pathologists as Addison's disease or as tuberculosis of the suprarenal glands. A positive clinical diagnosis of Addison's disease had been made in 23 of these cases, and a questionable diagnosis in 3; in the remaining 8 cases there were tuberculous lesions of one type or another. A second group of suprarenal glands adjudged to be normal was also observed for control. Both groups were subjected to roentgenologic examination. Of the 23 cases in which a positive diagnosis of Addison's disease had been made, 6 showed roentgenologic shadows of calcification; of the 3 questionable cases, 2 showed such shadows; of the 8 cases of tuberculous glands, 3 were positive. Thus 32.3 per cent of the entire group showed shadows of calcification. These types of calcification were noted: (1) Gross calcification of the entire gland; (2) multiple discrete areas of calcification; (3) homogeneous increased density of the entire gland, suggesting a diffuse deposition of lime salts. Twenty-three patients having Addison's disease clinically were then examined with the Roentgen rays and shadows indicative of suprarenal calcification were observed in 6.

Juvenile Paresis: Diathermy Hyperpyrexia in a Malaria Resistant Patient.—The case of a boy, aged 12 years, with all the diagnostic criteria of juvenile paresis, is reported by POLMER, from Touro Infirmary (*Arch. Phys. Ther., X-ray, Rad.*, 1933, **14**, 23). Vigorous antiluetic treatment and malarial therapy were employed for 11 months without any subjective improvement or objective signs indicative of arrest or remission. After receiving 12 diathermy hyperpyrexia treatments over a period of 6 weeks the spinal fluid was serologically negative on 2 successive examinations with an interval of 10 days between. The patient was discharged as improved 7 weeks after the series of treatments was commenced.

The Present Status of Electropyrexia.—Various methods of inducing hyperpyrexia are discussed and the techniques of diathermic, radiothermic and blanket electropyrexia are described by NEYMANN, FEINBERG, MARKSON and OSBORNE (*Arch. Phys. Ther., X-ray, Rad.*, 1932, **13**, 749). From their experience the authors conclude that, all other factors being equal, the diathermic procedure is the most efficient, the radiothermic next and that the electric blanket is least efficient. They consider the original type of blanket to be a dangerous instrument, because many of its wires are non-insulated and the patient may be burned deeply or electrocuted. A new blanket with insulated wires has been evolved and promises to be safe and efficient. About 60 per cent of the cases of general paresis given electrothermic treatment by the authors and others have been cured or improved, 75 per cent of a small series of patients suffering from multiple sclerosis have derived some benefit, 50 per cent of the authors' cases of asthma obtained long or short remissions and 85 per cent of a selected arthritic group were definitely benefited.

Diathermy in Gynecology.—According to CUMBERBATCH, of St. Bartholomew's Hospital in London (*Arch. Phys. Ther., X-ray, Rad.*, 1932, **13**, 782), a cure is confidently expected and almost always obtained from diathermy in gonococcal urethritis in women. Non-gonococcal cervicitis responds equally well to diathermy and the cervix regains its normal condition. In gonococcal arthritis application of diathermy to the cervix brings about relief of pain, reduction of swelling of the joints and increase of range of motion. Further benefit is obtained if the joints are subjected to diathermy, massage and movements. In non-gonococcal metastatic arthritis the same results are obtained in 75 per cent of the patients. In salpingitis, whether gonococcal or not, diathermy should not be administered if pus is present. If it is absent, diathermy causes all signs and symptoms to disappear. In dysmenorrhea of the congestive type in married women diathermy has not failed in any of the cases. On the other hand, it has done no good in cases of the spasmodic type.

The Value of the Roentgen Ray in the Diagnosis of Renal Tuberculosis.—In the opinion of WATERS (*Am. J. Roent. and Rad. Ther.*, 1933, **29**, 17) no investigation for renal tuberculosis is complete without satisfactory plain films and pyelograms of the urinary tract. The early Roentgen findings in renal tuberculosis are fringing of the calyces and possibly calcification in areas of cortical necrosis. The author's statistics show a diagnostic accuracy of 70 per cent in the pyelographic series. Areas of cortical calcification appeared on the plain film in 40 per cent of the cases of known tuberculosis. Direct smears yielded only 55 per cent of diagnoses, but guinea pig inoculations gave positive evidence in the other 45 per cent. There are no contraindications to pyelography in renal tuberculosis. Intravenous urography has not yielded the brilliant results expected, chiefly owing to the fact that sufficient concentration of the dye is lacking in so many cases, but with improvement in opaque media and technique, it is possible that great diagnostic accuracy may be achieved.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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Mental Reactions at the Climacterium.—JAMEISON and WALL (*Am. J. Psychiat.*, 1932, **9**, 895) state that the attitude and behavior of patients at the climacterium is uniformly one of depression, agitation and apprehension. Persistent restlessness, inability to sleep, occasional fretfulness and irritability of varying degree are noted. Suicide is more likely to occur than in any other type of illness and a general indifference to personal appearance and habits is common. These things are all easily recognized. The therapy for a frank case of melancholia is best managed in a hospital, although certain patients may be treated satisfactorily at home. Both physical and psychologic factors should be considered. The physical factors are very important and should receive careful attention. The excessive use of sedatives or opiates is contraindicated. Warm baths, warm packs, elimination of toxic features, regulated exercise, diet and healthy mental contacts are important. On the mental side, one who has the confidence of the patient may do much by a careful review of the history and a frank discussion of physiologic and psychologic forces at work. "Involutional melancholia is probably not a complete clinical entity in itself. The life history of the patient, including family tendencies, physical constitution, personality and psychic forces all have an influence. The period of the menopause with its physiologic changes forms the background for the play of these several factors. Any type of borderline or frank mental disease may appear at this time."

Mental Symptoms in Disseminated Sclerosis.—SALTHRE (*Norsk Mag. f. Lægevid.*, 1932, **92**, 353) states that of 2000 patients admitted to Vinderen Psychiatric Clinic between September, 1926, and December, 1930, 13 were diagnosed as cases of disseminated sclerosis. Of these, 12 were admitted for their psychic symptoms; 10 patients were females and 2 were males. In 8 the mental disturbances were severe, while the remaining 4 showed a mental state characterized by euphoria, slight dementia, pronounced emotional instability and egocentricity. The author suggests that, until a more specific etiology has been discovered, the term "psychoencephalitis" (invented by Ombredanne) should be applied to atypical cases of disseminated sclerosis with mental symptoms, as well as to similar cases of epidemic encephalitis and parencephalitis. The prognosis is grave; only 1 of Salthre's patients showed an almost complete recovery.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Production of Non-fatal Vascular Sclerosis in Rabbits by Means of Viosterol (Irradiated Ergosterol).—In a series of experiments carried out by SPIES (*Arch. Int. Med.*, 1932, **50**, 443) young rabbits were fed by stomach tube a preparation of viosterol, "10,000D," in doses of from 5 to 7 cc. at intervals of from 4 to 5 days. The period of administration including rests for recovery from toxic manifestations totaled from 40 to 70 days. After the final dose of viosterol the animals were killed from 97 to 102 days, and the organs were examined. The lesions found in these experiments situated in the aorta, lungs and kidneys are described and discussed in this paper. The aortas from the animals that had received viosterol showed severe medial sclerosis with varying degrees of hyalinization and calcification. In the kidneys the renal arteries and arterioles, and the renal tubules and glomerular capsules were hyalinized and calcified. Calcium was deposited in the parenchyma of the lungs, but was not seen in the pulmonary vessels. The author considers that these lesions were slightly less extensive than those found in a series of animals which he had previously studied, but that the relative proportion of hyalin degeneration to calcareous deposits was greater than in comparable lesions found in his former experiments. He suggests that the degree of calcification in these tissues was more extensive at some period during active treatment, but that in the interval between the cessation of viosterol administration and the termination of the experiments the animals may have reabsorbed some of the calcareous deposits, thereby leaving a permanent sclerosis of the aorta and vessels of the kidney.

A Functioning Tumor of the Islands of Langerhans.—BARNARD (*J. Pathol. and Bacteriol.*, 1932, **35**, 929) presents a case of an adenoma of the pancreas which appeared to have the function of secreting insulin. The patient complained of symptoms and presented signs of hypoglycemia, and was treated by considerable quantities of glucose. She recovered from several severe attacks but died 2 months later from the effects of hypoglycemia. Postmortem examination revealed an adenoma 1.2 cm. in diameter partly embedded in the head of the pancreas. The microscopic picture of this encapsulated mass led the author to believe this tumor to be an overgrowth of cells of the islets of Langerhans. It was considered benign, but was locally invading its own capsule. The author is certain that if the patient had agreed to operation, that removal of this functioning tumor would have resulted in a complete cure. It is pointed out, however, that the tumor would have been difficult to locate at operation, due to its position, but might have been found because of the firmer quality of the adenoma.

Calcified Corpora Amylacea in the Lung (Zur Pathogenese verkalkter Schichtungskugeln, Sog. "Corpora Amylacea," in der Lunge).—SCHILDKNECHT (*Virch. Arch.*, 1932, **285**, 466) reports a case of a paretic woman, aged 45 years, in which there was an unusually large number of corpora amylacea in the lungs; one-fifth to one-quarter of all the air sacs were plugged with the concretions, many of which were calcified. Roentgen ray plates taken a year before death showed miliary shadows through both lungs and gave rise to a diagnosis of miliary tuberculosis. (The Roentgen ray picture is in "Lehrbuch der Roentgen-diagnostik" by Schinz, Baensch and Friedl, 3d ed., vol. **2**, p. 798). The pathologic examination of the lungs showed a well-marked emphysema, chronic bronchitis and passive congestion. The corpora amylacea were visible and palpable in the gross; they measured up to 0.3 mm. in diameter; a large number of them completely filled the air sacs in which they lay and were adherent to the alveolar walls. They were composed of concentric layers built upon a small central nucleus. Sometimes the central nucleus was made up of anthracotic particles, sometimes of cells, sometimes of structureless débris. The lamina of the concretions varied in thickness and in staining qualities; many of the lamina stained deeply with hematoxylin and appeared to be made up of nuclear débris. These layers contained calcium and iron in appreciable quantities. Tests for amyloid were negative. The author believes emphysema favors the development of corpora amylacea; emphysematous air sacs do not readily empty themselves, tend to collect desquamated cells and secretions which form a coagulum and adhere in layers to a central nucleus. The development of multiple lamina probably takes considerable time. If the concretions lie in touch with the alveolar walls the lining cells become blended with the periphery of the concretion and form new lamina. No explanation is offered for the calcium and iron deposition within the concretions.

The Parallel Incidence of Filaria Bancrofti and the β-hemolytic Streptococcus in Certain Tropical Countries.—GRACE, GRACE and WARREN (*Am. J. Trop. Med.*, 1932, **12**, 493) report on the incidence of Filaria bancrofti and β-hemolytic streptococcus in Jamaica, B. W. I. Cultural examination of 100 consecutive abscesses showed that the streptococcus was responsible for only 6 per cent; 90 per cent were caused by the staphylococcus. Only 1 case of lymphangitis was seen, this occurring at intervals in a patient with an elephantoid lower limb. Only 3 cases of elephantiasis were found. They compare this low incidence of elephantiasis and lymphangitis with data obtained in British Guiana and St. Kitts, B. W. I., where a high incidence of the Filaria bancrofti and β-hemolytic streptococcus and their manifestations is found. They suggest that elephantiasis in the Caribbean tropics is associated with the presence of many minute foci of the β-hemolytic streptococcus in the corium of the affected part. They point out the rarity of intramuscular and multiple abscesses in Jamaica. In this paper the authors have shown the low incidence of Filaria bancrofti and β-hemolytic streptococcus and their manifestations in Jamaica as compared with the high incidence in St. Kitts and British Guiana. All three places are in the tropics where the Filaria bancrofti is supposedly endemic, the population largely colored and the requisite mosquito vector abounds.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Blood Cultures of Apparently Healthy Persons.—Numerous reports have been published on blood cultures from persons with various diseases, but the literature is meager concerning blood cultures from healthy persons. In studies on blood cultures in which control cultures have been reported, the incidence of negative cultures among the controls is usually high. Thus, Cecil, Nichols and Stainsby reported negative results in all of 54 control blood cultures made in connection with their work on arthritis. Gray and Gowen in similar studies obtained positive results in only 2 of 71 control blood cultures. One of these came from a patient with thrombosis of the cavernous sinus; the other, from a patient with agranulocytic angina. Cameron, Rae and Murphy recently cultured the blood of 100 healthy dental students and obtained 6 positive cultures, 4 of which yielded S. aureus and 2 diphtheroids. It is reasonable to assume that bacteria may enter the blood stream in persons who have acute or chronic infections. One would expect, therefore, with suitable methods, to be able to demonstrate bacteria in the blood stream in apparently healthy persons and theoretically, at least, would expect a higher incidence of positive results in cultures from persons with frank foci of infection. REITH and SQUIER (*J. Infect. Dis.*, 1932, **51**, 336) cultured samples of blood from 293 apparently healthy persons. Cultures containing streptococci, diplococci, diphtheroids, M. catarrhalis, colon bacilli and obligatory anaërobic rods were considered positive. Positive cultures were obtained from 53 (27 per cent) of 194 persons who had chronic focal infection, while positive cultures were obtained from only 12 per cent of 99 persons who had no demonstrable focus of infection. Pain in joints or muscles, including chronic infectious arthritis diagnosed clinically in 7, was present in 24. Ten (42 per cent) of these gave blood cultures positive for streptococci or diplococci. A seasonal variation in the incidence of positive blood cultures from persons without demonstrable foci of infection suggests that acute respiratory infections may be responsible for some of the positive cultures.

Epidemiology of the 1930 Poliomyelitis Epidemic in Kansas.—BROWN (*U. S. Pub. Health Rep.*, 1932, **47**, 1899) points out that acute anterior poliomyelitis is neither necessarily infantile nor paralytic, though called infantile paralysis. The epidemic of 1930 had about 3 times as many cases as in preceding epidemics, but the case death rate was much lower—9.2 per cent against about 30 per cent in earlier

outbreaks. August, September and October accounted for nearly all of the cases in the years studied. Males constituted 60 per cent of cases. Cases were reported in 433 families, but only 19 families had more than 1 case. The author has tabulated the various important symptoms in order of frequency, and also the site of paralysis. It is suggested that many non-fatal cases occur and are not recognized.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 15, 1933

Melanophores in Meninges of Mammals.—W. H. F. ADDISON and DORIS A. FRASER (Department of Anatomy, University of Pennsylvania). In examining the brains of gray Norway rats, both wild and captive, we have found melanotic pigment constantly present in the cranial meninges, and sometimes in the spinal meninges. In adult animals the pigment is readily visible when the brain is exposed. It is not evenly distributed, but is more abundant in definite areas. On the dorsal aspect of the brain the pigment is along the dural vessels between the cerebellum and cerebrum, and in the membranes behind the olfactory bulbs. It often forms a conspicuous area in the pia along the rhinal fissure. Ventrally it is seen throughout the base of the skull, ensheathing bloodvessels and nerves.

The pigment is in typical melanophores. These have a relatively small cell body and long branching processes, 6 to 8 or more in number. Where the melanophores are grouped together they have a syncytium-like appearance, with processes in seeming continuity with one another, but individual cells are also present. They seem to be an insert type of cell, when compared with the skin chromatophores of lower vertebrates.

In the newborn the pigment is not seen grossly. However, when shreds of the meninges are examined microscopically the melanotic cells are seen in certain areas. These cells are scattered diffusely, and do not show the orientation around bloodvessels as they do in the adult. The cells are smaller and are not as deeply colored as they are later on. The position of the nucleus is much more evident than in the adult because of the sparser distribution of the granules overlying it.

Pigment cells have been previously reported in the meninges of a small number of other mammals. Those include man, sheep, cow and baboon (Cynocephalus papio). In man they have been reported as especially evident in the meninges of Javanese and Egyptians, but are also found in Negroes, and to a less extent in Caucasians.

In the Norway rats, the pigment is present in all the color varieties which have been derived from it, such as gray piebalds, black piebalds and ruby-eye dilutes. These we have examined from the Wistar colony of Dr. Helen D. King.

Last year before this society, we reported pigmentation in the hypophyses and parathyroids of Norway rats. It would seem that there might be some relation between the pigmentation of the meninges and of the hypophysis, from their contiguity. But the several other species of mammals which have pigmented meninges do not appear to have melanotic cells in their hypophyses, with the possible exception of man. Therefore there seems to be no necessary correlation between the pigmentation of the meninges and of the hypophysis. And even if the pigmentation of the meninges were connected with that of the hypophysis, this would not explain the pigmentation of the parathyroids.

Glycogen Restoration After Exercise in Depancreatized Cats.—F. D. W. LUKENS, C. N. H. LONG and EDITH G. FRY (George S. Cox Medical Research Institute, University of Pennsylvania). MILROY (*Quart. J. Exper. Physiol.*, 1927, **17**, 161) and DEBOIS (*Archiv. Intern. de Pharmacodynamie et de Thérapie*, 1931, **91**, 65) have stated that the muscles of depancreatized animals do not restore the glycogen lost as a result of exercise. On the other hand, PESERICO (*Proc. XII International Congress of Physiology*) and CLEGHORN and PETERSON (*J. Physiol.*, 1932, **74**, 338) claim that such a restoration does occur.

In view of the importance of this question, not only for an understanding of the recovery process after exercise, but also for the mechanism of insulin action, we have reinvestigated this subject, and have attempted a more or less quantitative comparison of the amount and rate of glycogen reappearance in the muscles of both normal and depancreatized cats.

The animals were depancreatized some 8 to 18 days prior to the experiment. They were maintained on insulin, raw pancreas, meat and milk; 48 hours before use all insulin was withdrawn, and during the last 24 hours no food was supplied (water *ad lib.*). The normal animals were also fasted 24 hours before use.

For the experiment all were anesthetized by the intraperitoneal injection of "Nembutal." Both hind limbs were electrically stimulated, the same stimulus being used in all experiments. One limb was immediately frozen *in situ* with solid CO_2 and ether, and the other after various intervals of recovery. In order to obtain the initial glycogen value one fore limb was also removed. By previous experiments it was found that the ratio between the resting glycogen content of the hind and fore limbs was 1.3 to 1. This ratio was used in all experiments to calculate the initial level of glycogen in the hind limbs. It is important to know this value in each experiment in order to determine the amount of reduction of the glycogen due to the exercise, as from this reduction the glycogen reappearing during recovery can be expressed in terms that are comparable from animal to animal. This indirect method of calculation is rendered necessary by the wide variations in intial muscle glycogen content from animal to animal.

The results show quite clearly that the amount and rate of glycogen restoration are identical both in normal and depancreatized animals for periods of recovery of 1 and 2 hours. Approximately some 30 per cent of the glycogen lost has reappeared in this time. However, in some as yet uncompleted experiments where a period of 6 hours

recovery was observed, there appears to be a difference between the normal and depancreatized animals. The normal animals continue to lay down muscle glycogen, while in the depancreatized animals the amounts restored are of the same order as those observed in the 2-hour periods. This would indicate a division of the recovery mechanism into two parts in which the immediate one is independent of the presence of insulin, while the later stages require it.

In conclusion, however, it should be emphasized that considerable amounts of muscle glycogen can be formed in the depancreatized animal following exercise. The source of this glycogen remains conjectural.

Observations on Effort Angina.—L. B. LAPLACE and E. J. WAYNE (Department of Clinical Research, University College Medical School, London). Studies were made of approximately 450 induced attacks of angina pectoris in a group of 12 subjects who stated that the pain appeared only on physical exertion. Two subjects had aortic insufficiency, 4 had a history of sudden coronary occlusion and 6 appeared to be cases of coronary sclerosis. Two cases came to postmortem examination and showed extensive vascular calcification involving the left coronary artery.

Attacks were induced by causing the subjects to walk over a series of two steps until the onset of pain. Blood pressure, pulse rate and respirations were recorded continuously before and after exercise. Control experiments indicate that the pain appears after an amount of exercise which is relatively constant for each subject.

Blood pressure during the pain was often lower than during the pain-free period. It is concluded therefore that aortic dilatation cannot be the cause of the attack. The pulse rate was always elevated during the pain and lower during the pain-free period. In view of the fact that cardiac output is increased by exercise and that, other factors being equal, the O_2 consumption of the heart is known to increase in proportion to the pulse rate, this type of angina pectoris appears to be due to a relative coronary insufficiency in the presence of increased cardiac effort.

Digital pressure over the carotid sinus promptly lowered the blood pressure and slowed the pulse. When these effects were marked, the duration of the pain was significantly shortened. Intravenous injection of atropin sulphate, $\frac{1}{50}$ grain, greatly increased the pulse rate, diminished the amount of exercise necessary to produce pain, and increased the duration of the attack. These results indicate that either (1) the parasympathetic nerves are not vasoconstrictor to the coronary vessels, or (2) the increased work of the heart and not coronary spasm is alone responsible for the production of pain. The latter explanation is the more tenable.

Amyl nitrite shortened the duration of the attack in 10 cases. Nitroglycerin increased the amount of work necessary to produce pain in 7 cases and erythrol titranitrate acted similarly in only 2 cases. The blood pressure during the attack was usually lower than during control observations. The nitrites therefore appear to act only by causing coronary dilatation. The fact that they were not effective in all cases and that their effectiveness was proportional to the strength of the

drug indicated an organic obstruction of the coronary vessels (sclerotic, stenotic, etc.) and that coronary flow cannot be greatly increased by nitrite action in many cases.

No significant effect could be observed as a result of intravenous injection of Euphyllin or oral administration of alcohol. Repeated exercise did not appear to affect the duration of the attack or the amount of work necessary to produce it.

Anserine and Carnosine in Mammalian Skeletal Muscle.—W. A. WOLFF and D. W. WILSON (Department of Physiological Chemistry, University of Pennsylvania). Carnosine and the closely related anserine have been found in the skeletal muscles of a number of vertebrates. We have studied the distribution of these two imidazole derivatives by quantitative and by isolation procedures. We have isolated carnosine and anserine as copper salts from the skeletal muscles of the dog, cat, deer and opossum. The crystal form, composition and melting points were used in identification.

The carnosine and anserine content of certain muscles has been determined by a quantitative method recently reported by the present authors.[1] Horse and ox muscle are high in carnosine but contain little or no anserine; cat muscle has about equal amounts of carnosine and anserine; dog muscle is high in anserine but low in carnosine.

The occurrence of these two related compounds in vertebrate muscle suggests the possibility of an intimate metabolic relationship between the two and some physiological importance for this type of imidazole derivative.

Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities.—EUGENE M. LANDIS and JOHN H. GIBBON, JR. (Robinette Foundation, Hospital of the University of Pennsylvania). According to Poiseuille's law the volume of fluid flowing through a rigid tube is proportional to the fall in pressure along the tube. It seems possible, therefore, that if the peripheral fall in blood pressure could be increased the total amount of blood flowing past an arterial obstruction in unit time would be greater. The fall in pressure through the arterial tree may be increased physically in two ways, (*a*) by elevating aortic blood pressure or (*b*) by reducing peripheral blood pressure to a negative value. The first method is impracticable for numerous reasons but it is possible temporarily to reduce capillary and venous pressure by applying suction to the extremities.

An aluminium box was built large enough to accommodate the lower extremity to a point about 6 inches above the knee and strong enough to withstand pressures of -120 to $+120$ mm. Hg. A mercury manometer, communicating with the interior of the box, was equipped with electrodes so arranged that the one-half horse power motor operating an air pump was stopped through an electrical relay, whenever the pressure in the box exceeded or fell below atmospheric pressure by 120 mm. Hg. A valve was inserted between the pump and the box so that for 25 seconds the pump evacuated air from the box while for 5 seconds the pump expelled cooled air into the box.

[1] Journal of Biological Chemistry, 1933, **100**, p., cvi.

Alternate suction and pressure increased, by 45 to 78 per cent, the rate at which fluid flowed through a circulation schema. In normal subjects and patients the effects of suction and pressure on circulation were determined qualitatively by measuring skin temperatures under carefully controlled conditions.

In normal subjects it was found that alternate suction and pressure (*a*) diminished the rate of cooling of an extremity originally warm and (*b*) in the majority of instances caused an originally cold extremity to become conspicuously warmer. Suction and pressure sometimes failed to affect blood flow in a cold extremity when vasoconstrictor tone was extremely high. As soon as vasoconstrictor tone was diminished slightly blood flow was conspicuously and preferentially increased in the extremity exposed to positive and negative pressures.

The vasodilator response to warming one forearm was studied in normal subjects with and without the use of external pressure changes. It was found that alternate suction and pressure caused the vasodilator response to appear earlier and that the final temperatures reached were definitely higher in the extremity exposed to external pressure changes.

In patients with peripheral vascular disease alternate suction and pressure increased blood flow definitely even though organic obstruction had advanced to such a stage that no rise in skin temperature was obtained when vasoconstrictor tone was completely abolished by immersing both forearms in warm water or by anesthetizing the posterior tibial nerve.

To obtain the maximal effect on blood flow it is necessary to have (1) relatively brief periods of suction; (2) intermitting periods of pressure, and (3) diminished vasoconstrictor tone.

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